THE SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME DERIVATIVES OF CIS-TETRAHYDRO-FURANDIOL-3,4

A THESIS

Presented to

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by

James Perry Cleveland

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

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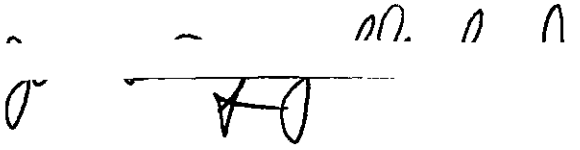

THE SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME DERIVATIVES OF CIS-TETRAHYDRO-FURANDIOL-3,4

Approved:

Chairman

Date approved by Chairman: 12/22/64

ACKNOWLEDGMENTS

I wish to thank sincerely Dr. James R. Cox, Jr. for suggesting this problem and for his constant encouragement and suggestions for its completion. I wish to thank Dr. D. S. Cain and Dr. P. B. Sherry for reading and criticizing the original manuscript and to thank the members of the research group for their helpful discussions and suggestions.

TO MY PARENTS

for their continued encouragement and support

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CHAPTER I

INTRODUCTION

A. Cyclic Five-Membered Phosphates

The reactivity of diesters of phosphoric acid in which there is present a hydroxyl group attached to the β-carbon atom has been found to be very much greater than the reactivity of those diesters which possess no such β-hydroxyl group (1,2,3). Brown and Todd first interpreted these results as involving cyclic five-membered triesters (3) which were subsequently and rapidly hydrolyzed. The formation of cyclic triesters of this type could easily explain the rapid basic depolymerization of the ribonucleic acids. The desoxyribonucleic acids, on the other hand, possess no such requisite hydroxyl group, and indeed are found to be relatively stable in base (4). The isolation of the presumed bicyclic intermediate mononucleotides (5,6) and the kinetic behavior of the independently synthesized mononucleotides gave strong support to this conclusion.

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(1) A. C. Bailly, Bull. soc. chim., France, [5], 9, 340, 405 (1942).

(2) E. J. Chargaff, J. Biol. Chem., 144, 455 (1942).

(3) D. M. Brown and A. R. Todd, J. Chem. Soc., 52 (1952).

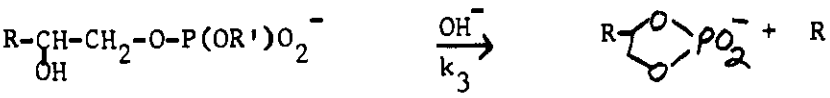
(4) J. R. Cox, Jr., and O. B. Ramsay, Chem. Rev., 64, 317 (1964).

(5) R. Markham and J. D. Smith, Nature, 168, 406 (1951).

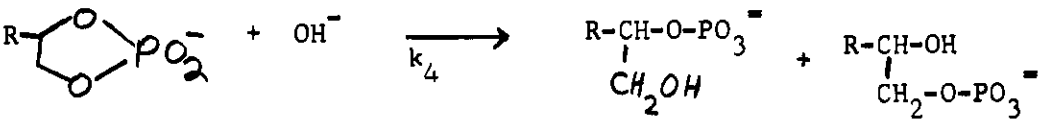
(6) R. Markham and J. D. Smith, Biochem. J., 52, 552 (1952).

However, O^{18} tracer studies on the hydrolysis of ribonucleic acid itself eliminated the possibility of a bicyclic triester (7) and pointed to a bicyclic diester as the intermediate monucleotide (I). The currently accepted pathway is illustrated in Figure 1 (4).

In connection with this proposed scheme Westheimer and coworkers (8) have studied the reactions of ethylene phosphate, the simplest such ester, and Brown and coworkers (9) have studied model systems for the proposed transesterification and hydrolysis reactions. (Eqs. 3, 4).



(Eq.3)



(Eq.4)

In all cases reported with the model systems the rate-determining step is ring closure ($k_4 >> k_3$); in contrast to these observations the fast step in ribonucleic acid hydrolysis is ring closure ($k_1 >> k_2$), presumably due, at least in part, to the more favorable geometry of the cis-hydroxyl group present on the ribose sugar ring (Figure 1).

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(7) D. Lipkin and P. T. Talbert, J. Am. Chem. Soc., 76, 2871 (1954).

(8) See J. R. Cox, Jr. and Ramsey, Chem. Rev., 64, 317 (1964).

(9) Ibid., ref. 33, 34, 41.

B Represents the Organic Bases Adenine, Uracil, Cytosine, and Guanine.

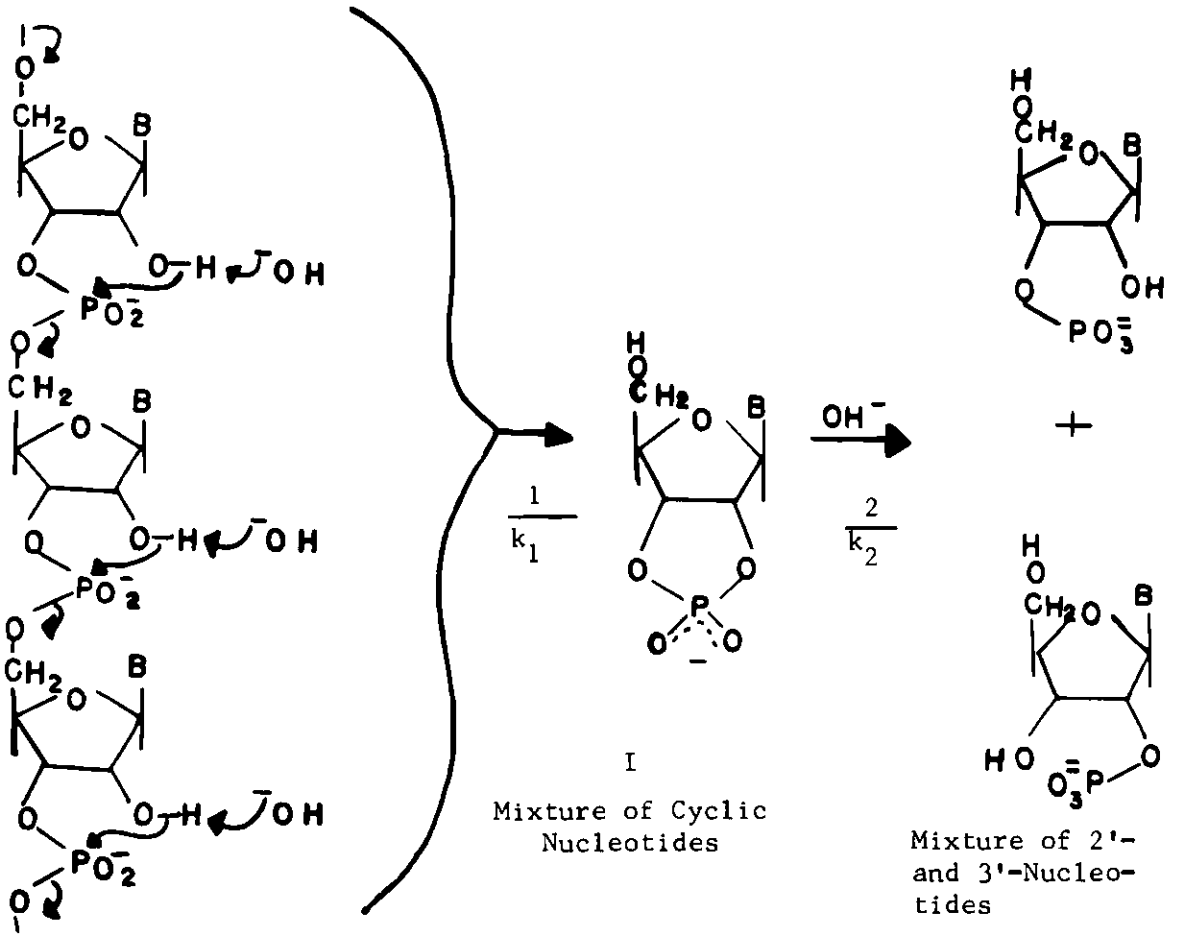
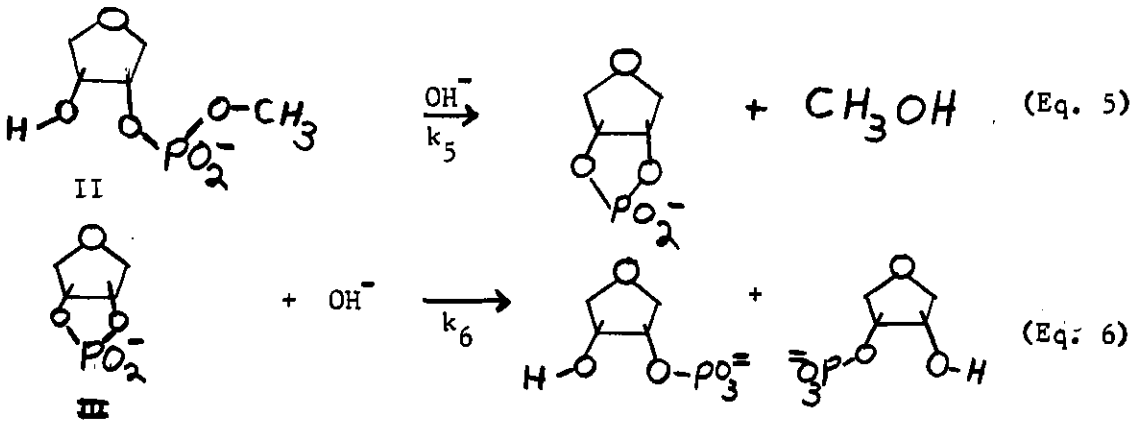


Figure I. Hydroxide Ion-catalyzed Hydrolysis of a Ribonucleic Acid

Several independent groups of researchers have studied the alkaline hydrolysis of ethylene phosphate, and all agree that it is hydrolyzed approximately 10^8 times faster than the corresponding acyclic analogue, dimethyl phosphate (4). Cox and Guida (10) have studied the model compounds (II) and (III) and found with these compounds, as with the ribonucleic acids, the fast step to be ring closure ($k_5 > k_6$) although, in contrast to the ribonucleic acids, both steps proceed at very nearly the same rate (Eqs. 5 and 6).



(Eq. 5)

(Eq. 6)

Cox, Wall, and Westheimer (11, 4) compared the heats of alkaline hydrolysis of methyl ethylene phosphate and dimethyl-2-hydroxyethyl phosphate and observed that the cyclic ester released about 5.5 kcal per mole more energy than the acyclic analogue, indicating that the large reactivity of the cyclic compound is in part associated with thermodynamic strain present in the five-membered ring. This energy difference, however, is not large enough to account for the unusually large reactivity difference between the cyclic five-membered esters (e.g.

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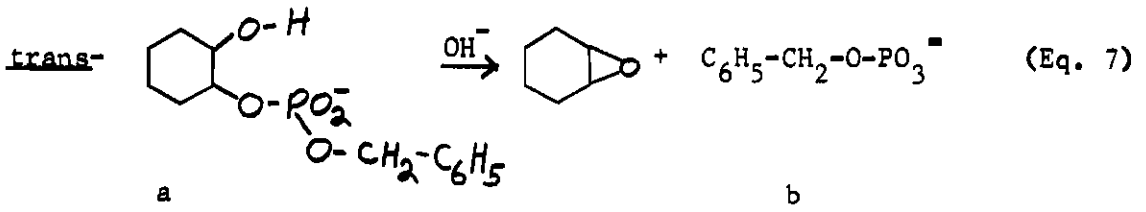
(10) J. R. Cox, Jr. and J. H. Guida, unpublished results.

(11) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, Chem. Ind. (London) 929 (1959).

ethylene phosphate) and the simple acyclic analogues (e.g. dimethyl phosphate); other factors, therefore, must be present serving to enhance the rate of hydrolysis of the cyclic compounds over that of the acyclic esters. Neither the model compounds II and III nor the ribonucleic acids themselves have yet been studied thermodynamically. Wickersham and Cox (12) have studied the effects of possible backbonding (13) between oxygen and phosphorus in the cyclic five-membered compounds although no one has reported a study of the geometry in solution of any of the five-membered ring esters. The conformations of the ribose sugar ring in the ribonucleic acids and the mononucleotides, and of the tetrahydrofuran ring in the model compounds II and III are unknown. It has been observed that (a), when treated with base, yields the epoxide (b) in 67% yield (eq. 7) (14,15).



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(12) T. W. Wickersham, M.S. Thesis, Georgia Institute of Technology (1964).

(13) See M. Panar, E. T. Kaiser, and F. H. Westheimer, J. Am. Chem. Soc., 85, 602 (1963).

(14) D. M. Brown and N. K. Hamer, J. Chem. Soc., 406 (1960).

(15) See also D. M. Brown and D. A. Usher, Proc. Chem. Soc., 309 (1963).

No such reports of epoxide formation have appeared with either the ribonucleic acids or the tetrahydrofuran derivatives II and III. The strong possibility therefore exists that the geometry of the ribose ring in the nucleic acids and of the tetrahydrofuran ring in the model compounds, II and III, plays an important role in the observed reactivity of these compounds, both with regard to their rapid alkaline hydrolysis and also with respect to their relative kinetic behavior compared to ethylene phosphate.

B. The Nuclear Magnetic Resonance Spectroscopy Technique

In 1959 Karplus (16) reported a theoretical equation relating the vicinal coupling constant $J_{HH'}$ to the H-C-C'-H' dihedral angle in ethane. Using a valence - bond approach he arrived at equation (8) (Figure 2).

$$J = A + C\cos 2\phi \qquad \text{(Eq. 8)}$$

A, B, and C were constants and, ϕ was the H-C-C'-H' dihedral angle. For a C-C bond length of 1.543Å, sp^3 hybridization at carbon, and an average energy of 9 ev., he calculated the constants to be A = 4.22 cps, B = -0.5 cps, and C = 4.5 cps. As Karplus himself pointed out (16,17), this equation is an approximate relationship; the effects of different C-C bond lengths, hybridizations at carbon, and electronegativities of substituents were neglected. Conroy (18) performed a similar

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(16) M. Karplus, J. Chem. Phys., 30, 11 (1959).

(17) M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963).

(18) H. Conroy, "Advances in Organic Chemistry," Vol. II, Inter-Science, New York, N. Y., (1960), page 265.

calculation employing the molecular orbital method and obtained a theoretical curve quite similar to the one obtained by Karplus; the details, in particular a discussion of the limitations of this work, however, have not appeared. A great deal of work employing Karplus' equation in conformational studies of molecules in solution has been published in the recent literature (19, 19c) and several groups

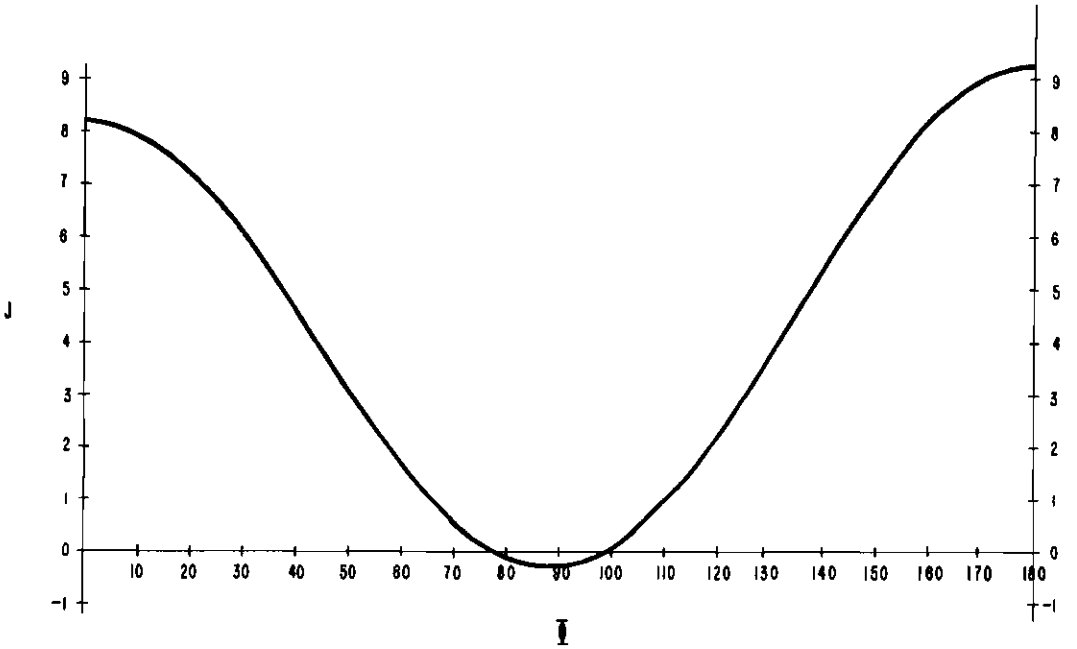

Figure 2. The Karplus Equation

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(19) See (a) R. F. Heck, J. Am. Chem. Soc., 85, 2016 (1963); (b) A. K. Bose, ibid., 85, 2795 (1963); (c) K. L. Williamson, W. S. Johnson, ibid., 83, 4623 (1961); (d) C. D. Jardesky, ibid., 83, 2919 (1961); (e) N. J. Leonard, R. A. Laursen, ibid., 85, 2072 (1963); (f) R. W. Lenz, J. P. Heeschen, J. Polymer Sci., 51, 247 (1961); (g) R. J. Abraham, K. L. McLauchlen, Mol. Phys., 5, 513 (1962), for further references.

of investigators have attempted to improve on the original equation (20, 21, 22).

Within a given series of structurally similar compounds the major cause of deviation from the Karplus relationship should be the variation in the electronegativities of the substituent groups (i.e. the hybridization at carbon and C-C bond lengths should remain virtually constant, cf. ref. 25,26). Bothner-By and Glick (23) observed quite early that the vicinal coupling constants in a series of ethyl and isopropyl derivatives were functions of the Huggins electronegativity (24) of the attached groups. These workers were able to fit their observed data to equations (9) and (10) for the ethyl and isopropyl compounds, respectively.

$$J_{HH'} = 8.4 - 0.14E \qquad \text{(Eq. 9)}$$

$$J_{HH'} = 8.4 - 0.55E \qquad \text{(Eq. 10)}$$

E, Huggins electronegativity

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(20) See Discussion Faraday Soc., 34, 115 (1962), a review with other references.

(21) See M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963) reference 6.

(22) J. Powles, Discussion Faraday Soc., 34, 30 (1962).

(23) R. E. Glick and A. H. Bother-By, J. Chem. Phys., 25, 362 (1956).

(24) M. L. Huggins, J. Am. Chem. Soc., 75, 4123 (1953).

(25) K. L. Williamson, J. Am. Chem. Soc., 85, 516 (1963).

(26) P. Laszlo and P. von R. Schleyer, ibid., 85, 2709 (1963).

Since this first paper by Bother-By and Glick, there have been several reports of attempts to correlate quantitatively the observed vicinal coupling constants with the electronegativities of various substituents (17, 20, 25, 26, 27, 28). Some of these correlations have been fairly successful within a series of compounds in which a change in the substituent in question yields virtually no change in carbon hybridization or C-C bond distance. However, at the present time there exists no way of accurately applying these electronegativity dependencies to other molecules not falling within one of the several series studied. These dependencies can provide a basis, though, for the qualitative estimation of the effect a given substituent should have on the vicinal coupling constant.

Although much attention has been focused upon the correlation of electronegativity and vicinal coupling parameters, much less effort has been directed toward the understanding of the effects of carbon hybridization and C-C bond length changes on these parameters. There is currently a controversy concerning the magnitude of these effects. Bothner-By and Naar-Colin (29) and Elridge and Jackman (30) have

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(27) J. S. Waugh and S. Castellano, J. Chem. Phys., 35, 1900 (1961).

(28) T. Schaefer, Can. J. Chem., 40, 1 (1961).

(29) R. E. Glick and A. A. Bothner-By, J. Am. Chem. Soc., 83, 231 (1961).

(30) J. A. Eldridge and L. M. Jackman, Proc. Chem. Soc., 89 (1959).

accumulated experimental data suggesting that these effects are relatively small compared to the electronegativity perturbations; in contrast to these observations, other workers have presented evidence that the vicinal coupling constants are quite sensitive to hybridization and bond length changes (26, 19a, 31, 32). Thus, the true size of the effect of varying hybridizations and bond lengths remains unknown, although Karplus (17) indicates that $J_{HH'}$ should decrease as the H-C-C' bond angle increases for a given H-C-C'-H' dihedral angle, and likewise a decrease in $J_{HH'}$ for an increase in the C-C bond length is to be expected.

Although quantitatively accurate correlations between vicinal coupling constants and H-C-C'-H' dihedral angles are at the present time impossible, qualitatively good conclusions can be drawn if caution is used in the correlations. In particular, if measurements are made on compounds which have C-C bond distances and carbon atom hybridizations closely approaching the tetrahedral values and if the electronegativity effects of the various substituents are reasonably estimated, the dihedral angles thus obtained should present a qualitatively good picture of the conformation of the molecule under study. Likewise, if the correlations are carried out for a series of structurally quite similar molecules, and if a reasonable correction is made for the different electronegativities of the various substituents, then the relative conformations thus obtained should be fairly good. If, on

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(31) O. L. Chapman, J. Am. Chem. Soc., 85, 2014 (1936).

(32) J. A. Graham, and M. T. Rogers, ibid., 84, 2249 (1962).

the other hand, the relationship is employed taking into account none of the errors involved, the conclusions drawn from such a study must be taken lightly.

It is the purpose of this work to synthesize several compounds belonging to the two structural classes represented by the model compounds II and III and, by analyzing their nuclear magnetic resonance spectra for chemical shifts and coupling constants, to apply the Karplus relationship in determining qualitatively the conformations of the tetrahydrofuran ring in solution in each of these two classes of compounds.

CHAPTER II

EXPERIMENTAL

Instrumentation

All melting points were obtained using a modified Hershberg melting point apparatus equipped with a motor driven stirrer and Anschutz thermometers. The melting points are uncorrected.

All infrared (IR) spectra were recorded with a Perkin-Elmer Infracord spectrophotometer and calibrated with the 6.238 μ band of polystyrene.

The Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian A-60 spectrometer utilizing tetramethyl silane as an internal reference with organic solvents and sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal reference with aqueous solvents. All chemical shifts (δ) are given in cycles per seconds (cps) downfield from the internal reference.

The theoretical NMR spectra were calculated on a Burroughs B-5000 computer using a program written by Mr. Wayne G. Sullivan and Mr. Walter Fleming.

The sample of barium cis-tetrahydrofuran-3,4-diolcyclic phosphate, III, was kindly donated by Dr. James R. Cox, Jr. (NMR: See Fig. 15); the sample of cis-tetrahydrofuran-3,4-dibenzoate, (V), was kindly given by Mr. Ken Rice (NMR: See Fig. 16).

All compounds and organic solvents not specifically described below were obtained commercially and used without further purification.

Meso-erythrytol (33)

Five-hundred grams (5.7 mole) of butene-2-diol-1,4 and 0.3 g. of osmium tetroxide were dissolved in 500 ml. of water. To this solution was added with vigorous stirring 300 ml. (5.0 mole) of 30 per cent hydrogen peroxide; the pot temperature was held between 25 and 32°. After the addition was complete, 2 g. of zinc dust was added to reduce the osmium oxides, and the resultant mixture was filtered. The filtrate was stripped under vacuum (aspirator) below 50° until a thick syrup was obtained. The addition of an equal volume of methanol to this syrup yielded crude crystals of the desired product. The crystals were removed by filtration and the process repeated until no further meso-erythrytol could be obtained from the reaction mixture. The crude product was easily purified by recrystallization from methanol. Yield: 415 g. (60%).

cis-Tetrahydrofuran-3,4-diol (IV) (34)

Seventy-three grams (0.6 mole) of meso-erythrytol and 1 g. of p-toluenesulfonic acid were mixed in a round bottom flask set up for distillation and heated under vacuum. The mixture began to melt at

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(33) W. Reppe, et al., Ann. 596, 137 (1955).

(34) C. O. Edmonds, U. S. Patent, 2, 572, 566; C. A., 46, 6157 (1952).

about 120°, and the pyrolysis proceeded very rapidly at 140°. The diol distilled over cleanly at a pot temperature between 140 and 150°. The product was redistilled to remove the small amount of water present. B.p. 111-112°/0.5 mm, 117-118°/1.5mm, Yield: 41.0 g. (67%). (IR and NMR; see Figs. 3 and 4, respectively.)

Trimethyl Borate (VIII) (35)

One hundred and ninety-two grams (6.0 mole) of methanol and 62. g. (1 mole) of boric acid were refluxed together for twelve hours, and the 1:1 trimethyl borate-methanol azeotrope was removed by distillation through a vacuum jacketed column, b.p. 54-55°/1 atm;; lit. 54°/750 mm. A white, crystalline, solid residue, presumably unreacted boric acid, remained after distillation. The resulting azeotrope was separated by saturating the solution with lithium chloride whereupon almost pure trimethyl borate separated as the top layer of a two phase mixture. The purification was completed by distillation, the product being carefully protected from the atmosphere. B.p. 68-69°/1 atm.; lit. 68°/750 mm. Yield: 36.4 g. (35%).

3-Methoxy-2,4,7-trioxa-3-borabicyclo(3.3.0.)octane (VIII)

Nine and four-tenths grams (0.09 mole) of cis-tetrahydrofuran-3,4-diol and 9.4 g. (0.09 mole) of trimethylborate were mixed and allowed to stand for 15 minutes with occasional shaking. Upon removal of the methanol formed (observed b.p., 64°), a white, crystalline solid ap-

(35) H. I. Schlesinger, H. C. Brown, D. L. Mayfield, and J. R. Gilbreath, J. Am. Chem. Soc., 75, 213 (1953).

peared which could be purified either by distillation under vacuum or by sublimation. Sublimation was preferred as the distilled product crystallized in the condenser and was difficult to remove. The material was always protected from atmospheric moisture by means of a drying tube filled with silica gel. M.p. 55-56°; b.p., 60-61°/2.5 mm. Yield: quantitative. Anal. calc. for $C_5H_9O_4B$: C, 41.72; H, 6.26; Found: C, 42.14; H, 6.50. (IR and NMR: see Figs. 5 and 6, respectively).

2,4,7-Trioxa-3-sulfitobicyclo(3.3.0)octane (IX)

Nine and two-tenths grams (0.08 mole) of thionyl chloride was added dropwise to 8.0 g. (0.08 mole) of cis-tetrahydrofuran-3,4-diol; a vigorous exothermic reaction ensued with the evolution of copious quantities of hydrogen chloride gas. Upon completion of the addition, a white solid crystallized. This solid was purified easily both by sublimation and recrystallization from water, followed by drying under vacuum. M.p., 112.5-113.5°. Yield: quantitative if purified by sublimation. Anal. calc. for $C_4H_6O_4S$: C, 32.00; H, 4.00. Found: C, 31.99; H, 3.81. (IR and NMR: see Figs. 7 and 8, respectively).

2,4,7-Trioxa-3-carbonatobicyclo(3.3.0)octane (X)

To a solution containing 19.2 grams (0.185 mole) of cis-tetrahydrofuran-3,4-diol and 18.6 g. (0.370 mole) of triethyl amine was added 0.05 g. of sodium metal. The sodium dissolved very slowly. After dissolution was complete the solution was chilled in an ice bath, and an excess of phosgene liquid was added with vigorous stirring. An immediate exothermic reaction took place yielding a

thick,reddish-brown paste. The crude reaction mixture was warmed to room temperature and then placed under vacuum (aspirator) for 15 minutes to remove any excess phosgene. At the end of this period no odor of phosgene could be detected.

The crude product was dissolved in hot benzene and the undissolved triethyl amine hydrochloride was removed by filtration. On cooling, triethyl amine hydrochloride crystallized out of the benzene filtrate and was removed by filtration. The addition of a slight excess by volume of pet. ether caused the carbonate to crystallize out as long, red needles. The crude carbonate was then filtered, placed under vacuum to remove all solvent, and sublimed to yield a white, crystalline solid; m.p., 69.0-70.5°. Yield: 2.2 g. (10%). Anal. calc. for $C_5H_6O_4$: C, 46.08; H, 4.62. Found: C, 46.08; H, 4.62. (IR and NMR: see Figs. 9 and 10, respectively.)

3,3-Dimethyl-2,4,7-trioxabicyclo(3,3,0.)octane (XI)

One hundred grams of sodium sulfate was added to a solution of 10.4 g. (0.1 mole) of cis-tetrahydrofuran-3,4-diol dissolved in 125 ml. of acetone containing three drops of con. hydrochloric acid. The resultant mixture was then stirred for four days being carefully protected from atmospheric moisture by means of a silica gel drying tube. At the end of this time the sodium sulfate was removed by filtration, and the excess acetone was distilled off at atmospheric pressure. The crude product was then distilled under vacuum with very little decomposition, yielding a colorless liquid. B.p., 52-53/7.0 mm. Yield: 9.1 g. (63%). Anal. calc. for $C_7H_{12}O_3$: C, 58.53; H, 8.33. Found: C, 59.40; H, 8.87. (IR and NMR: see Figs. 11 and 12, respectively).

cis-Tetrahydrofuran-3,4-diacetate (VI) (36)

Ten and four-tenths grams (0.1 mole) of cis-tetrahydrofuran-3,4-diol and 0.1 g. of sodium acetate were dissolved in a 100 per cent by weight excess of acetic anhydride, and the resulting solution was refluxed for five days. At the end of this time the solution had a dark brown color due to the decomposition of the diol and the ester. The excess acetic anhydride was distilled off under vacuum (aspirator), and the crude product was then distilled under vacuum. This product was then redistilled under vacuum to remove the slight trace of water present. B.p., 66-67°/0.04 mm; 85-86°/0.6 mm; lit., 66-67°/0.04 mm. Yield: 16.1 g. (86%). (IR and NMR: see Figs. 13 and 14, respectively).

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(36) E. J. Hedgley and H. G. Fletcher, J. Am. Chem. Soc., 86, 1576 (1964).

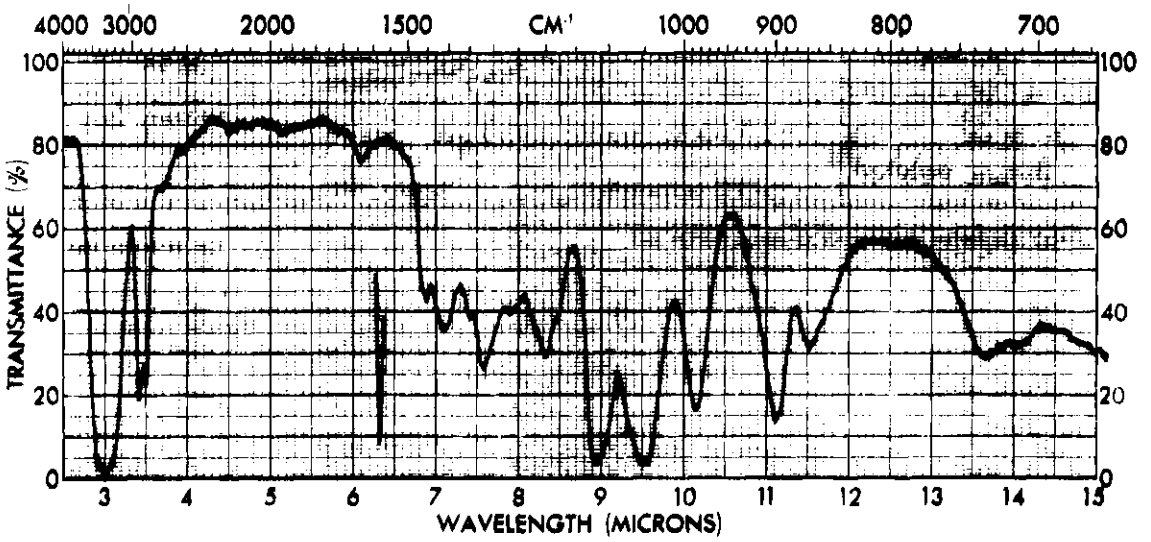


Figure 3. IR of diol, IV (neat)

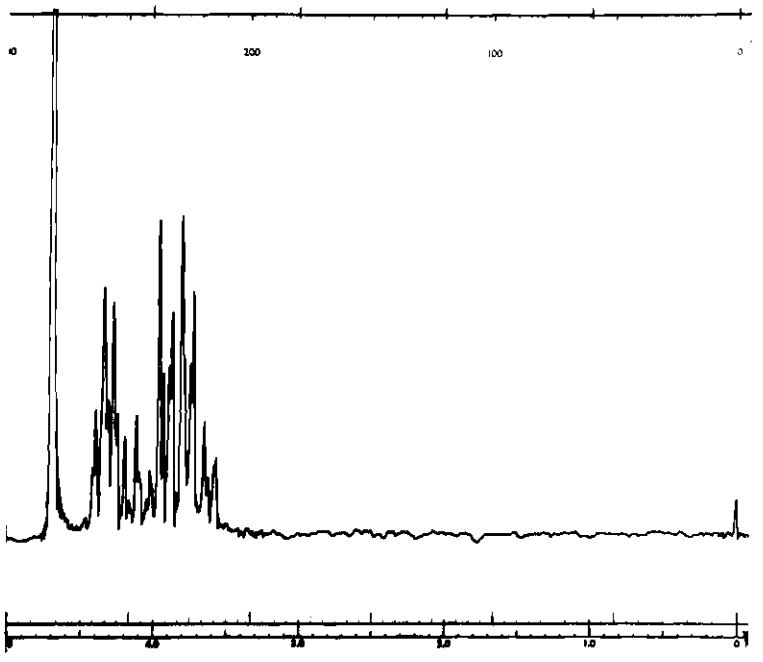


Figure 4. NMR of diol, IV (neat)

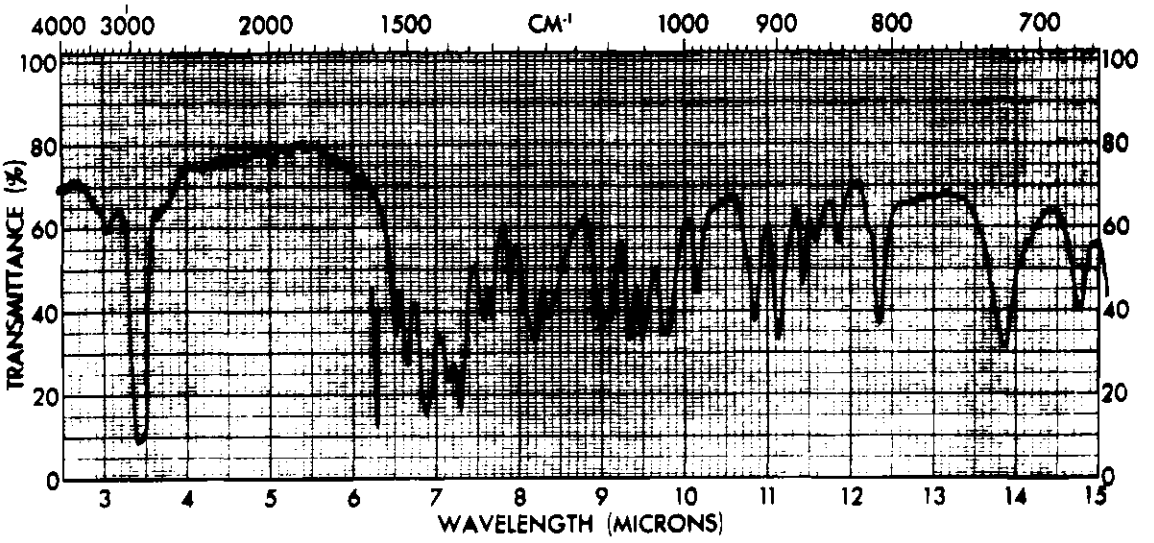


Figure 5. IR of borate, VIII (Nujol)

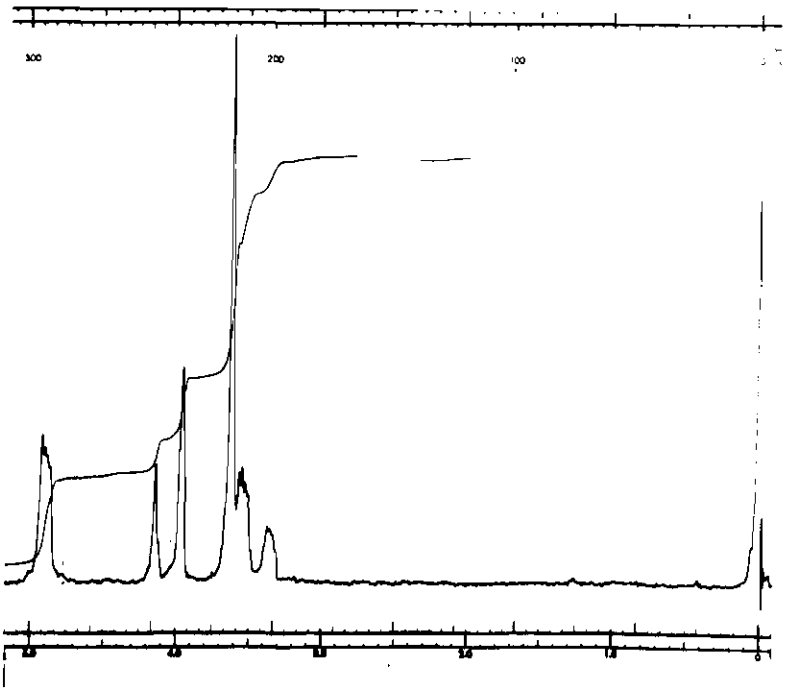


Figure 6. NMR of borate, VIII (chloroform)

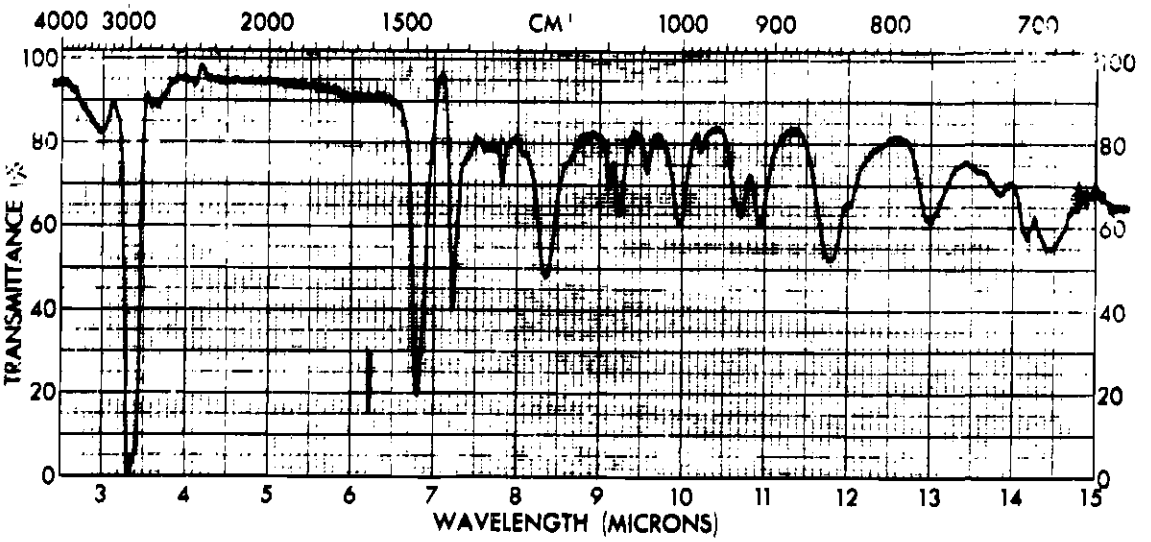


Figure 7. IR of sulfite, IX (Nujol)

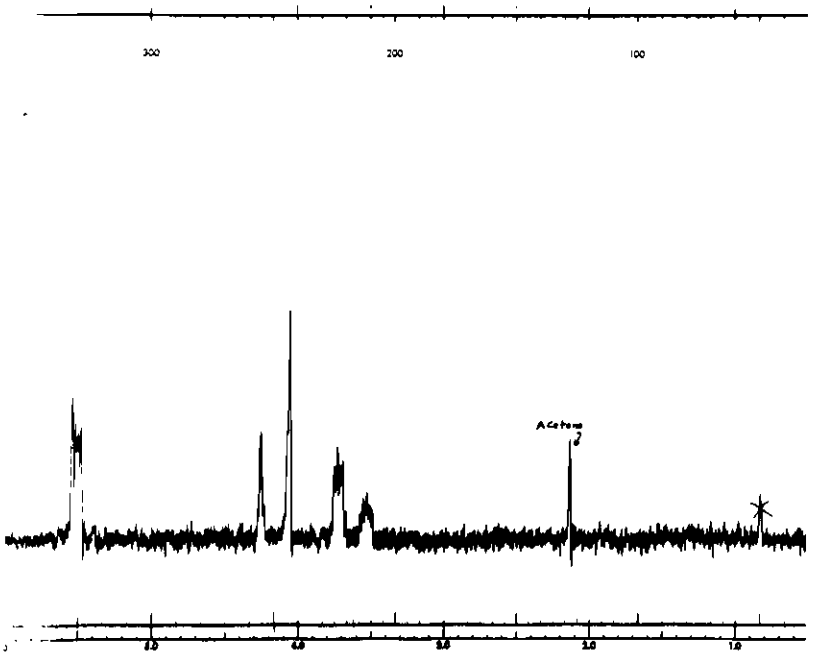


Figure 8. NMR of sulfite, IX (chloroform)

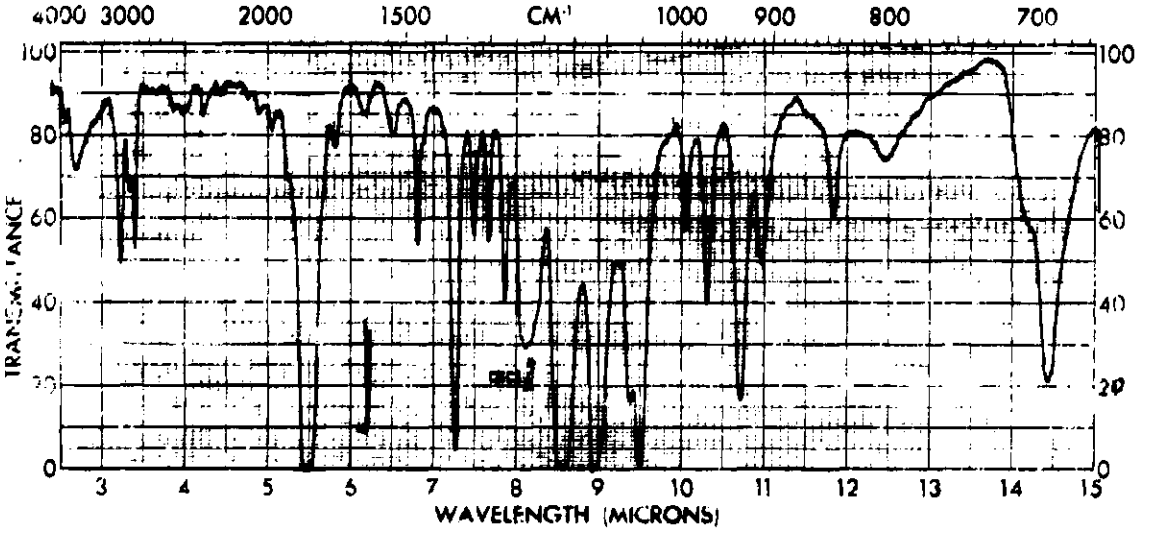


Figure 9. IR of carbonate, X (chloroform)

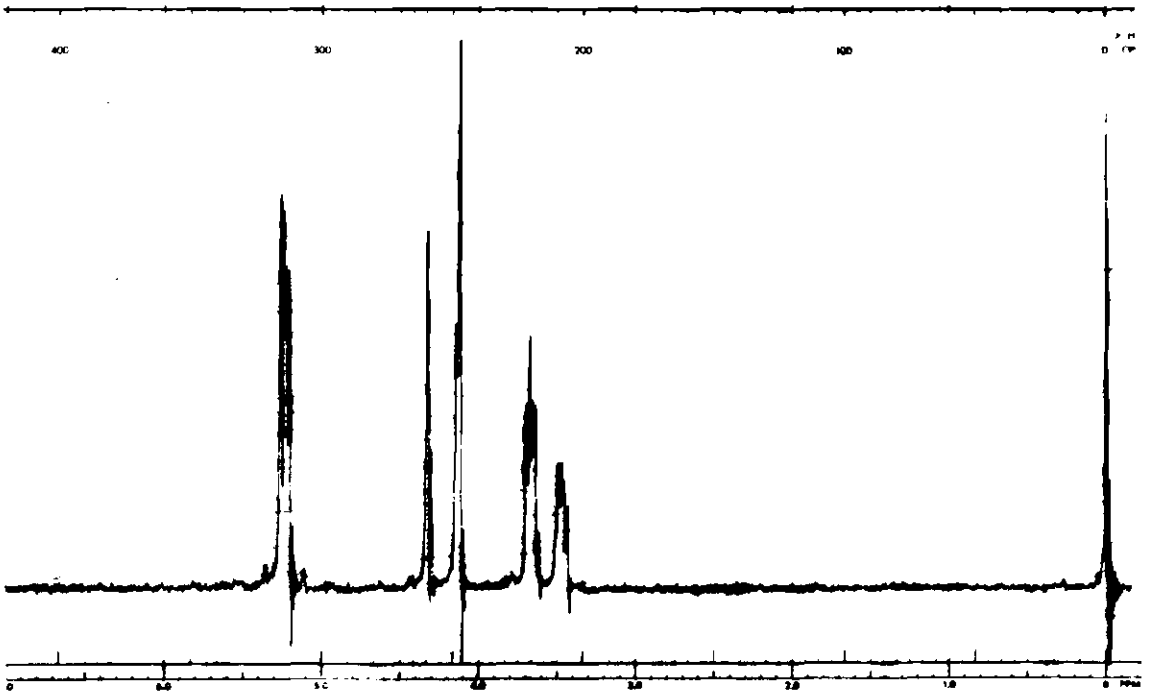


Figure 10. NMR of carbonate, X (chloroform)

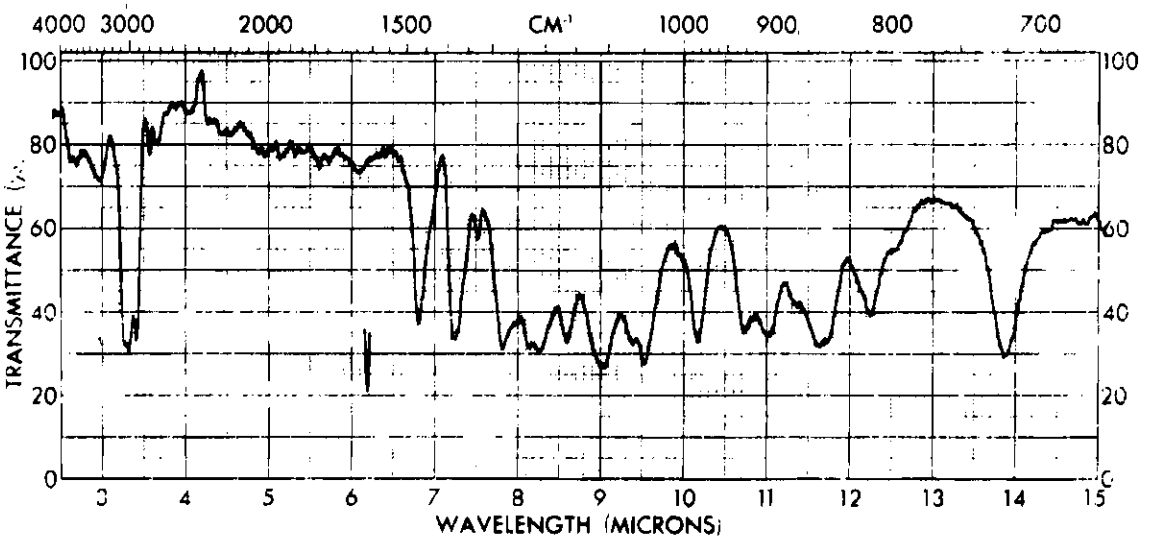


Figure 11. IR of ketal, XI (neat)

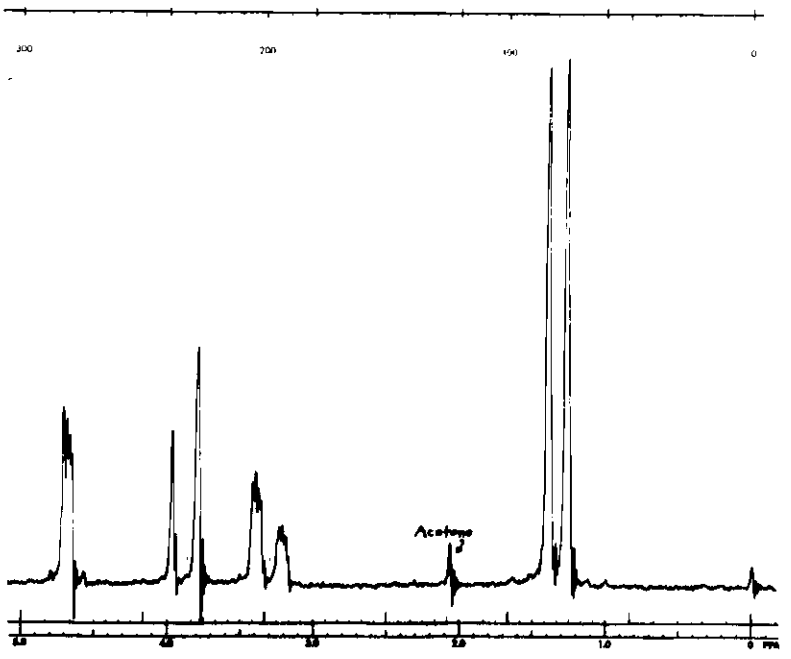


Figure 12. NMR of ketal, XI (neat)

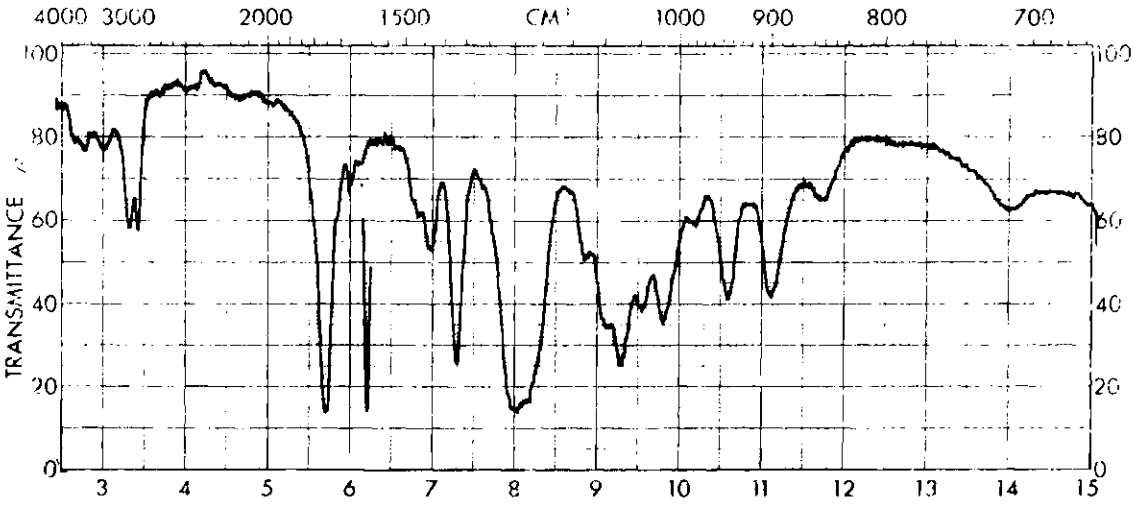


Figure 13. IR of diacetate, VI (neat)

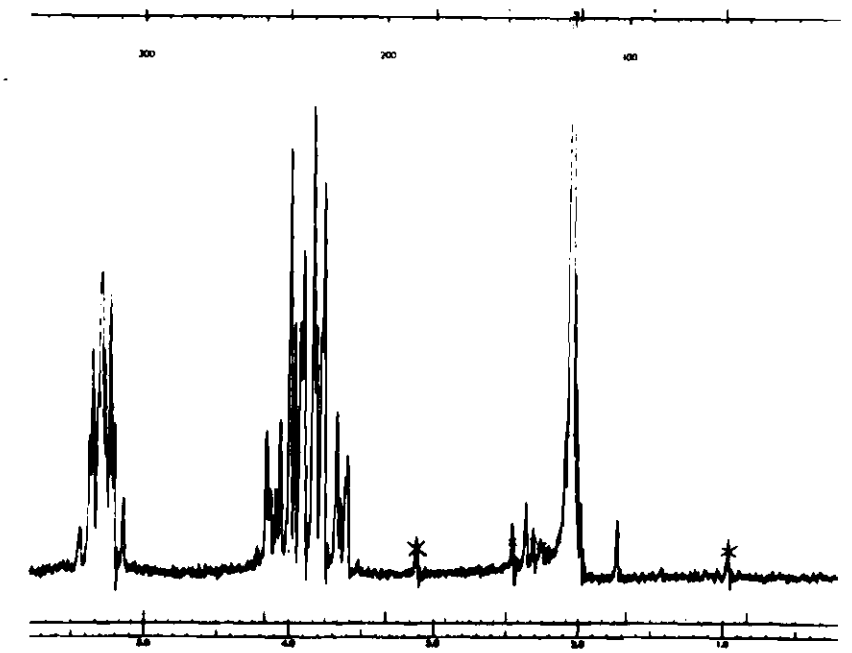


Figure 14. NMR of diacetate, VI (neat)

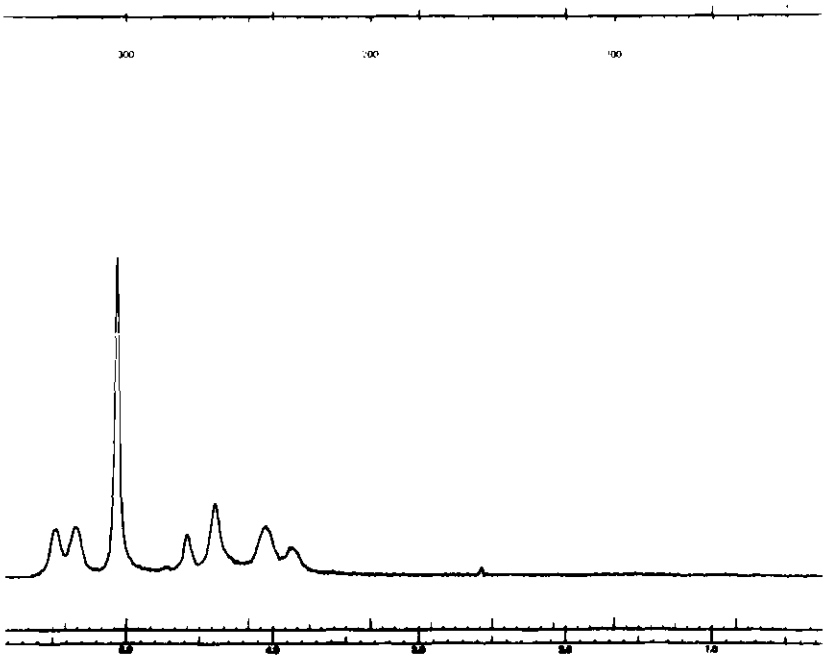


Figure 15. NMR of phosphate, III (D 20)

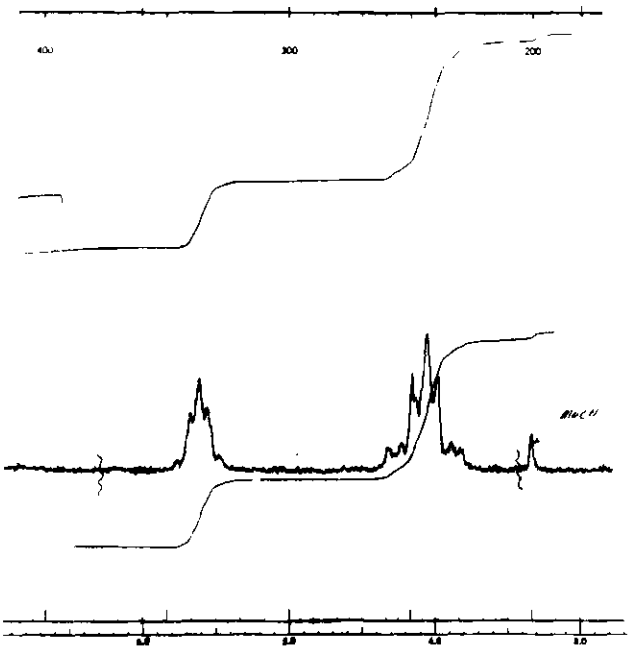


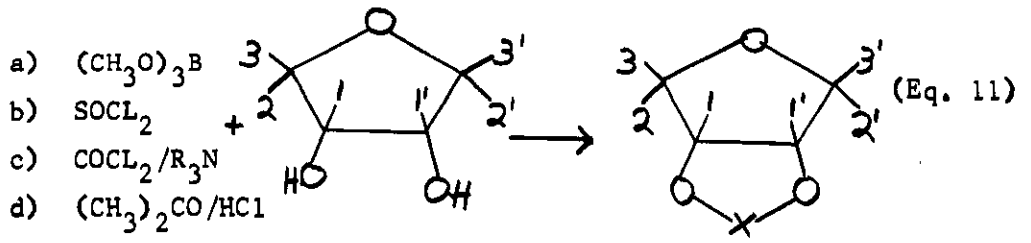
Figure 16. NMR of dibenzoate, V (carbon tetrachloride)

CHAPTER III

RESULTS

The compounds studied are represented by structures III, IV, VI, VIII, IX, X, and XI. (For the sake of simplicity these will hence-forth be referred to as the phosphate, III, diol, IV, diacetate, VI, borate, VIII, sulfite, IX, carbonate, X, and ketal, XI.) The borate, sulfite, carbonate, and ketal have previously not been reported; the others are known compounds (34, 36).

Except for the phosphate (see experimental) all the bicyclic compounds (borate, sulfite, carbonate, ketal) were prepared by the general type of reaction given by equation (II).



(Eq. 11)

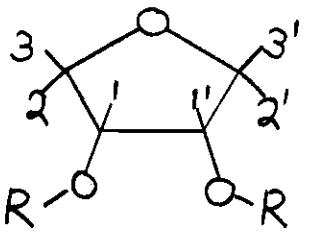
X: a) B-O-CH_3 (VIII)

b) C=O (IX)

c) C=O (X)

d) $C(CH_3)_2$ (XI)

The structure of the phosphate, III, corresponds to $X=PO_2^-$. The synthesis of the diol, IV, and diacetate, VI, are described in Chapter II; the dibenzoate, V, was donated by Mr. Ken Rice.



R: a) -H (IV)

b) $-COC_6H_5$ (V)

c) $-COCH_3$ (VI)

The structures of the previously unreported compounds were confirmed on the basis of their analyses, mode of synthesis (above), IR and NMR spectra, and hydrolysis products. In the IR, none of the new compounds shows an -OH absorption band in the 2.8 - 3.5μ region whereas they all possess a band between 9.1 and 9.3μ , characteristic of a tetrahydrofuran ring (37). The carbonate shows a strong band at 5.55μ (C = O stretch) and the sulfite possesses a strong absorption at 9.15μ (S=O stretch). Treatment of the borate, sulfite, and carbonate with aqueous base yields the diol (38), identified by its NMR spectrum (Fig. 3). In the presence of acid the ketal is hydrolyzed to the diol and acetone.

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(37) "The Infra-red Spectra of Complex Molecules"; L. J. Bellamy, John Wiley and Sons, New York, N. Y., 1958.

(38) Note: The borate is hydrolyzed very rapidly by pure water; the sulfite, however, must be refluxed with concentrated base for several hours before hydrolysis is complete.

Since the bicyclic molecules are not planar, they should each possess three distinct types of magnetically non-equivalent hydrogen. The NMR spectrum of each of these five compounds (Figs. 6, 8, 10, 12, and 15) shows three separate multiplets with an integral ratio of 1:1:1, in agreement with the structures of these molecules. Reasoning from the general effect of substituent electronegativities on chemical shifts (δ) (39), the low field multiplet is assigned to protons 1 and 1' ($\delta_1 = \delta_{1'}$) the mid-field "doublet" (40) to protons 2 and 2' ($\delta_2 = \delta_{2'}$), and the quite complicated upfield "doublet" (40) to protons 3 and 3' ($\delta_3 = \delta_{3'}$) (41). Due to the large uncertainty in assigning electronegativities to the methyl borate, sulfite, phosphate, carbonate, and isopropylidene groups, no quantitative correlation between group electronegativities and chemical shifts could be obtained. However, one would expect the electronegativities of the various acid groups to follow qualitatively the order of sulfite$\geq$ phosphate$>$ carbonate$>$ isopropylident$>$ methyl borate. On the basis of this relative order, one would expect the 1 and 1' protons to be the most affected by varying the acid groups in the bicyclic esters. This is observed with all of the compounds studied. The effects of the

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(39) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 14-20. Other references are given here.

(40) "Doublet" is used here to describe the general appearance of the multiplets and does not imply that fine splitting is absent.

(41) See structures VIII, IX, X, XI, for numbering.

varying electronegativities on the 2 and 2' and 3 and 3' protons, however, are more difficult to assess since these protons are much farther away from the electronegative group than are the 1 and 1' protons, although the 2 and 2' and 3 and 3' protons would be expected to be affected much less than the 1 and 1' protons due to this larger separation. In any case, one would predict that increasing the electronegativity of the acid portion of the esters would increase the chemical shifts of the analogous protons in each of the bicyclic esters. This is also observed. The errors involved in obtaining the chemical shifts of the 2 and 2' and 3 and 3' protons (see page33) preclude the discussion of the relative effects of the varying electronegativities of the acid groups on the 2 and 2' protons versus the 3 and 3' protons. Recourse to a Dreiding model, however, clearly shows that the 2 and 2' protons are closer to the esterifying acid group in each of these molecules than are the 3 and 3' protons. The 2 and 2' protons should, therefore, be less shielded than the 3 and 3' protons, and hence absorb at lower applied field strengths than the 3 and 3' protons. The possibility of predominant diamagnetic anisotropic shielding by the carbonyl group in the carbonate is discounted on the grounds that the chemical shifts of the carbonate protons are qualitatively those which would be predicted from the relative order of electronegativities given above.

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(42) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, Co., Inc., New York, N. Y., 1959, Chap. 6. The notation used in this work is that found in this reference.

The absorption signals due to protons 2 and 3 (2' and 3') show the pattern of a perturbed AB (42) system, the perturbations on protons 2 and 2' differing from those on 3 and 3'. The low field multiplet of the phosphate is further complicated over the analogous multiplets of the other bicyclic compounds by the $P\text{-}H_1$ and $P\text{-}H_{1'}$ interaction across three bonds ($J_{P\text{-}H_1} = J_{P\text{-}H_{1'}} = 8.0$ cps.). The other protons in the phosphate molecule, being five bonds away from the phosphorus atom, do not interact with this atom to any observable extent. Also, the borate shows an $O\text{-}CH_3$ peak at 216.5 cps., and the ketal shows two $C\text{-}CH'_3$s at 75.5 and 83.0 cps. (43). Other than these exceptions, the patterns of the spectra of all five bicyclic compounds are the same, differing only in the relative chemical shifts of the analogous protons and, to a small degree, in the various coupling constants. This consistent, identical pattern, by analogy with the spectrum of the phosphate (a known compound), lends further strong support to the structures assigned to these molecules.

The chemical shifts and geminal coupling constants (J_{gem}) for the five bicyclic molecules are listed in Table 1. The chemical shifts of the 1 and 1' protons were obtained directly from the experimental spectra; those of the 2 and 2' and 3 and 3' protons for all the bicyclic compounds except the carbonate were calculated using the relationship given by Equation (12).(44).

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(43) These results are in agreement with the data given by L.M. Jackman, reference (39), Chapter 4, pages 54-59.

(44) Reference (42), Chapter 6, page 120.

$$(2\text{-}4) - (1\text{-}3) = (\delta_{AB}^2 + J_{AB}^2)1/2 \qquad \text{(Eq. 12)}$$

(2-4) is the spacing in cps. between lines 2 and 4 in the observed spectrum (etc. for lines 1 and 3). This equation applies to a simple AB pattern (42), and the values obtained from it for these molecules are therefore only approximately correct. To obtain the exact 2 and 2' and 3 and 3' chemical shifts, however, requires a tedious, trial-and-error calculation; this calculation was performed for the carbonate, and the chemical shifts and coupling constants for this ester are correct within experimental error. Table 2 gives the calculated coupling constants for the carbonate; Figure (17) shows the comparison of the calculated versus experimental spectrum (sweep width, 50 cps.).

Table 1

Chemical Shifts and Geminal Coupling Constants for the Phosphate, Borate, Sulfite, Carbonate, and Ketal, in cps. $\delta_1 = \delta_{1'}$, $\delta_2 = \delta_{2'}$, $\delta_3 = \delta_{3'}$

Compound	δ_1	δ_2	δ_3	J_{gem}
Phosphate	324	268	238	-11
Borate	294	243	208	-9.5
Sulfite	331	249	219	-11
Carbonate	314-.5	252±.5	215±.5	-11.4±.2
Ketal	282	231	198	-10.0

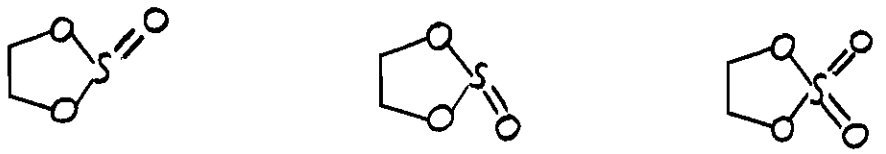
The calculations were performed by placing the coupling constants and unperturbed chemical shifts into the computer which then did the actual numerical calculation and printed out the spectrum derived from these values. The sign of J_{23} ($J_{2'3'}$) was taken as negative (45) although a positive J_{gem} yielded essentially the same calculated spectrum.

Table 2

Coupling Constants for the Carbonate, in cps.

$J_{11'}$	= 7.00 ± 0.2	$J_{33'}$	= 0.00
$J_{12(1'2')}$	= 0.35 ± 0.2	$J_{1'3(13')}$	= 0.00
$J_{13(1'3')}$	= 3.50 ± 0.2	$J_{1'2(12')}$	= 0.00
$J_{23(2'3')}$	= -11.50 ± 0.2	$J_{23'(2'3)}$	= -1.10 ± 0.2

The sulfite, IX, may actually be a mixture of two isomers corresponding to the S=O group's being either up or down; ethylene sulfite has been shown to exist in these two forms (c) and (d) (Fig. 18). (46).



(c) (d) (e)

Figure 18. The two forms of ethylene sulfite and ethylene sulfate.

(45) See C. N. Banwell and N. Sheppard, Discussions Faraday Soc., 34, 115 (1962) for a discussion of relative signs of coupling constants.

(46) J. G. Pritchard and P. C. Lauterbur, J. Am. Chem. Soc., 83, 2105 (1961).

The NMR spectrum of ethylene sulfite shows the pattern of an A_2B_2 system brought about by the slow (or non-existent) interconversion between the (c) and (d) forms giving rise to two pairs of magnetically non-equivalent protons. Ethylene sulfate (e), on the other hand, gives only one sharp peak in the NMR as all of the protons in this molecule are magnetically equivalent. No attempt was made to show that the sulfite, IX, exists as a mixture of two separate isomers; the NMR of IX does not clarify this point.

The NMR spectra of the diol, diacetate, and dibenzoate are given in Figs. (4), (14), and (16). These three spectra, which differ sharply from those of the bicyclic esters, all contain two complicated multiplets with an integral ratio of 2:1, the upfield multiplet having the largest integral. As seen in Figs. (4) and (14), acetylation of the diol shifts the downfield multiplet 59.5 cps. to lower fields whereas the upfield multiplet is shifted by only about 3 cps. to lower field (measured from the center of each pattern). On the basis of this observation (43) and the reasoning pertaining to peak assignments given above, the low-field multiplet is assigned to protons 1 and 1' ($\delta_1 = \delta_{1'}$) and the upfield multiplet to protons 2 and 2' ($\delta_2 = \delta_{2'}$) and 3 and 3' ($\delta_3 = \delta_{3'}$) (47). As with the carbonyl group of the carbonate, there is here no evidence for a predominant diamagnetic anisotropic shielding by either the acetate carbonyl groups in the diacetate or the two phenyl rings in the dibenzoate.

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(47) See structures IV, VI, and V for proton.numbering.

The chemical shifts for protons 1 and 1' in all three of these molecules can be extracted directly from the observed spectra by measuring the center of the low-field multiplet. The chemical shifts of the 2 and 2' and 3 and 3' protons, however, cannot be obtained directly from the experimental spectra due to the complexity of the pattern and the small difference in chemical shifts between protons 2 and 2' and 3 and 3' in all threee esters. The sole method for obtaining the correct values of the 2 and 2' and 3 and 3' chemical shifts is to perform a tedious, trial-and-error calculation as done with the carbonate, the difficulty of which is particularly enhanced by the large uncertainties in estimating δ_2·($\delta_{2'}$), and δ_3($\delta_{3'}$), and J_{gem}. This calculation was performed for the diacetate, and the chemical shifts are listed in Table 3. The other values found in Table 3 are the chemical shifts of the 1 and 1' protons (read directly from the experimental spectra) and the centers of the upfield multiplets for the diol and dibenzoate. The correct coupling constants for the diacetate are listed in Table 4.

With the diacetate, as with the carbonate, J_{23}($J_{2'3'}$) was taken as negative although here also a positive geminal coupling constant gave essentially the same calculated spectrum as a negative J_{gem} (45). Figure (19) shows the calculated versus the experimental spectrum for the diacetate (sweep width, 100 cps.).

The effect of J_{12} on the calculated spectra of both the diacetate and the carbonate should be noted. This virtual coupling (48)

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(48) See J. I. Musher and E. J. Corey, Tetrahedron, 18, 791 (1962) and P. Laszlo and P. von R. Schleyer, J. Am. Chem. Soc., 86, 1171 (1964) for further discussion and references.

Table 3

Chemical Shifts for the Monocyclic Esters in cps. $\delta_1 = \delta_{1'}$, $\delta_2 = \delta_{2'}$, $\delta_3 = \delta_{3'}$

Compound	δ_1	δ_2	δ_3
Diacetate	317.5 .5	250.0 .5	224.3 .5
Diol	258	ca. 233	ca. 233
Dibenzoate	338	ca. 244	ca. 244

Table 4

Coupling Constants for the Diacetate

$J_{11'} = 5.4 \pm 0.2$	$J_{33'} = 0$
$J_{12(1'2')} = 5.6 \pm 0.1$	$J_{1'3(13')} = 0$
$J_{13(1'3')} = 4.2 \pm 0.1$	$J_{1'2(12')} = 0$
$J_{23(2'3')} = -9.6 \pm 0.1$	$J_{23'(2'3)} = 0$
$J_{22'} = 0$	

between protons 3, 5, and 2 (4, 6 and 1) serves to complicate the patterns of all multiplets in both spectra, the degree of complication de-

pending upon the magnitude of J_{12}. However, the width of none of the calculated multiplets is altered by J_{12} values ranging from zero to 17 in the calculated diacetate spectra and zero to 12 in the calculated carbonate spectra. If J_{12} is taken equal to zero in the calculated diacetate spectrum, the complete pattern has the form of an ABC system; in the calculated carbonate spectra, however, a zero value for J_{12} does not reduce the complete pattern to a simple ABC case due to the complications arising from the interactions across four bonds. Although these intereactions across four bonds are equal to zero in the diacetate spectrum they are not zero in the carbonate spectrum and, indeed, J_{23}, ($J_{2'3}$) is rather large compared with other proton-proton coupling constants across four bonds.

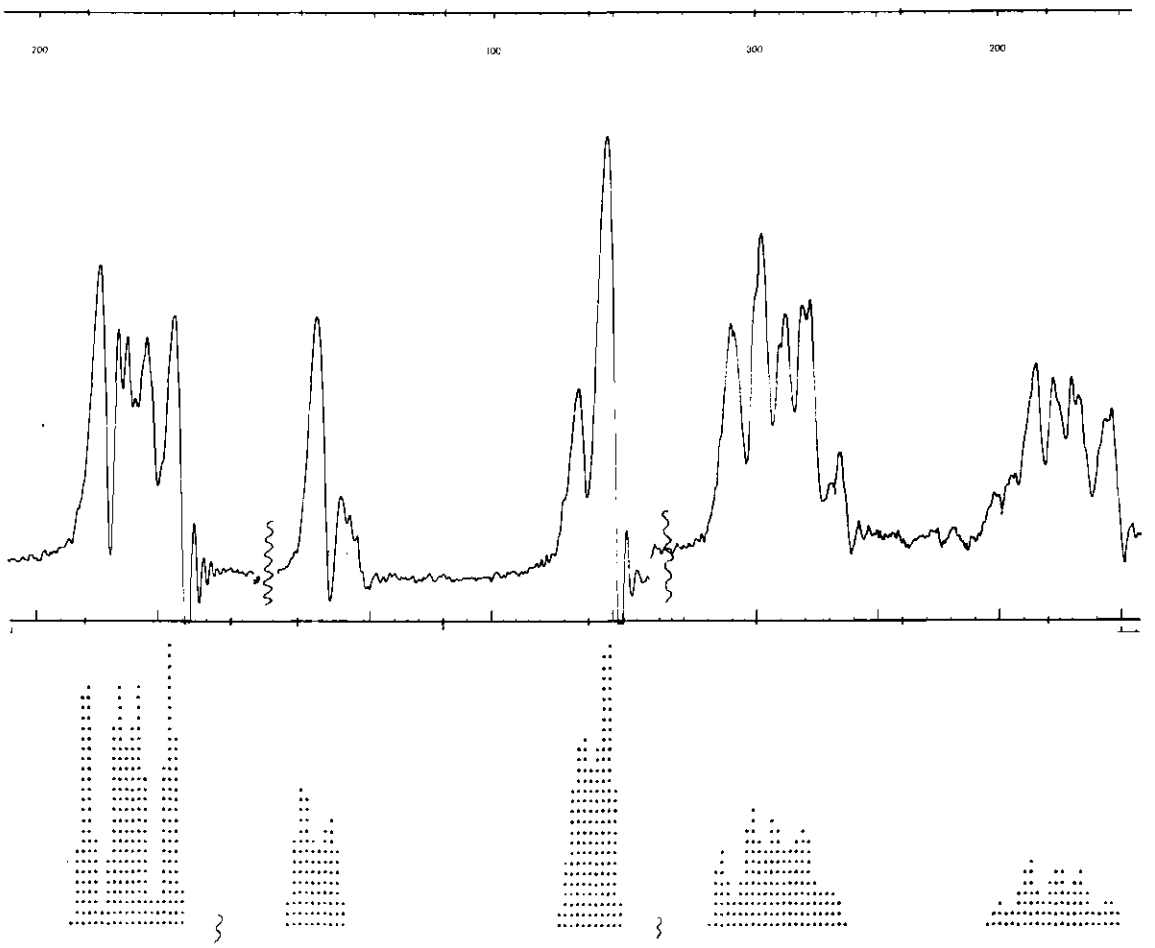

Figure 17. Above, experimental NMR spectrum of the carbonate (50 cps.); below, calculated NMR spectrum of the carbonate (50 cps).

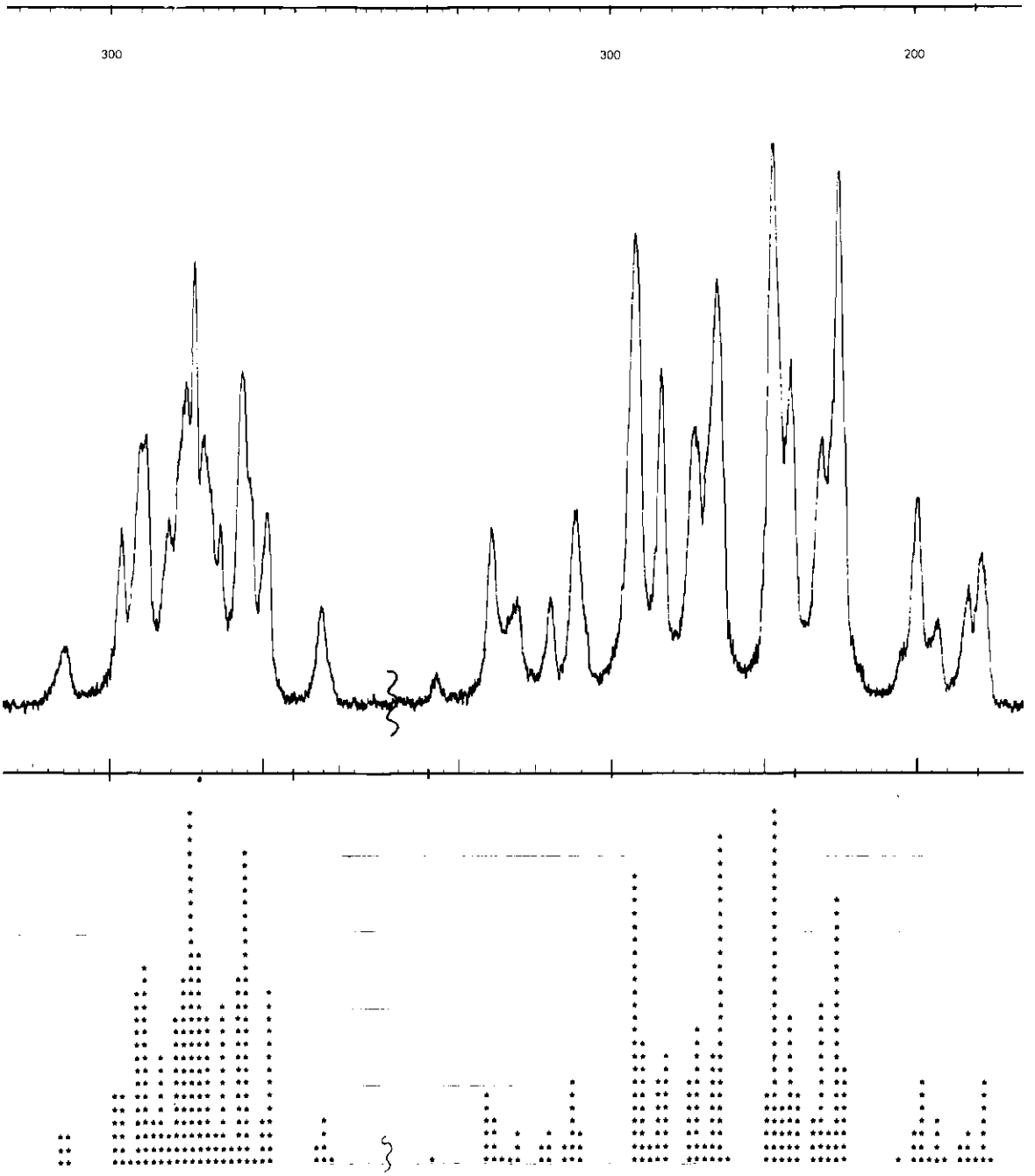

Figure 19. Above, experimental NMR spectrum of the diacetate (100 cps); below, calculated NMR spectrum of the diacetate (100).

CHAPTER IV

CONCLUSIONS

It is obvious from the discussion in Chapter I B that the use of uncorrected coupling constants to obtain dihedral angles from the Karplus equation can give rise to fallacious conclusions. This is especially true for the compounds in the diacetate and carbonate series as each proton-bearing carbon atom is bonded to an oxygen atom in either an ester or ether linkage. Thus, in order to draw qualitatively valid conclusions, the effects on the various coupling constants of these groups due to their electronegativities must be estimated. Since there is at this time no information pertaining to either the C-O or C-H bond lengths or the carbon atom hybridizations in molecules of these types, it must be assumed that these values are close to those used by Karplus in his derivation. This may or may not be a good assumption.

There are many reports of attempted correlations between vicinal coupling constants and substituent electronegativities. The data of Williamson (25) and of Laszlo and Schleyer (26), however, appear to offer the best method for estimating the magnitude of these corrections since these workers have studied the effects of group electronegativities versus vicinal coupling constants in the saturated part of a series of norbornene derivatives. Williamson has even observed that the magnitude of the electronegativity perturbation is indeed a function

of the orientation within the molecule of the perturbing substituent, although there is no way of estimating the overall size of the perturbation in a series of molecules of unknown conformation (49). Both Williamson and Laszlo and Schleyer were able to obtain a fair agreement between vicinal coupling constants and the electronegativity values taken from the work of Dailley and Cavanaugh (50). Williamson found that the acetate group (electronegativity = 3.8) decreased the predicted coupling constant (based on the Karplus equation) J_{BX} in (XII a) by 7.3 per cent. Similarly, a hydroxyl group (electronegativity = 3.43) lowered the predicted coupling constant in (XII b) by 9.7 per cent. On this electronegativity scale an ether lingage has a value of 3.37 and would consequently be expected to have approximately the same effect on the vicinal coupling constant, J_{BX}, as both the acetate and the hydroxyl group. In the diacetate, then, one might predict that the observed vicinal coupling constants have been decreased by about 17 per cent (9.7 + 7.3) and that the value to be substituted into the Karplus equation should be 6.5, 5.1, and 6.8 cps for J_{11}, J_{12}, and J_{13}, respectively. However, Williamson also reported J_{AX}(XIIa) to be 2.5 cps, in constrast to a predicted 2.1 cps for the unsubstituted compound. This complication was not explained.

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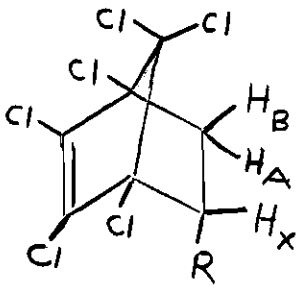
(49) See also D. H. Williams and N. S. Bhacca, J. Am. Chem. Soc., 86, 2742 (1964)

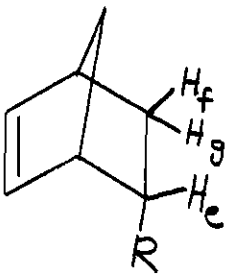
(50) B. P. Dailley and J. R. Cavanaugh, J. Chem. Phys., 34, 1099 (1961).



R: a) O-CO-CH_3

b) -O-H

XII



R: a) O-CO-CH_3

XIII

Laszlo and Schleyer, using the same electronegativity scale, reported a J_{efin} (XIIIa) of 7.9 cps, a 3.6 per cent lowering from the predicted value; unfortunately J_{eg} was not given. On the basis of these, assuming approximately the same effect from the ether linkage as above, the perturbations should amount to about a 13 per cent lowering of the predicted values. The corrected values would then be 6.2, 4.8, and 6.4 cps. for $J_{11'}$, J_{12}, and J_{13}, respectively.

Fortunately, the estimated adjustments from both sets of data yield corresponding corrected coupling constants which are nearly the same. Substitution of both sets of corrected values into Karplus' equation yields corresponding angles which differ from each other by only a few degrees. There is no guarantee, however, that the corrections used are valid for the diacetate series of compounds. Likewise, it should be pointed out that an extrapolation of the data of both

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(51) The value for hydrogen, Pauling's scale. See ref. (26).

Williamson and also Laszlo and Schleyer to an electronegativity of about 2.1 (51) does not yield a vicinal coupling constant of 8.2 cps, as predicted by theory. This observation along with Williamson's result that Jax in (XIIa) is larger than predicted by theory (at present) can not be satisfactorily explained. These deviations may be due to the orientations of the perturbed substituents, different bond lengths and hybridizations than those used by Karplus in his derivation, or indeed a combination of these effects operating simultaneously. It is reasonable, however, to assume that the observed vicinal coupling constants for the diacetate should be lowered relative to the theoretical values predicted by the Karplus relationship. Likewise, in view of the data of Williamson and Laszlo and Schleyer, as well as those of other workers (19, 21, 22), it is reasonable to assume that the coupling constants observed for the diacetate have been lowered by approximately eight to 17 per cent. Applying these corrections and averaging the results, one obtains the dihedral angles given in Table 5.

Table 5

Vicinal Coupling Constants and Dihedral Angles for the Diacetate

	J. Uncorrected	J. Corrected, Average	Dihedral Angle
J_{11}	5.4	6.2	29° ± 6°
J_{12}	4.2	4.9	137° ± 6°
J_{13}	5.6	6.4	27° ± 6°

It should be noted that a variation in the three corrected coupling constants by as much as ± 0.6 cps yields a change in the corresponding angles by no more than ± 6°. These variations in coupling constants correspond to corrections between approximately four to 26 per cent to $J_{11'}$, two and 31 per cent to $J_{12'}$, and four and 25 per cent to $J_{13'}$. The dihedral angles listed in Table 5, therefore, should probably be correct within the error given. Also noteworthy is the fact that these dihedral angles yield an H_2-C-H_3 bond angle of 110°.

The reasoning applied to the diacetate can also be applied to the carbonate although the lack of specific knowledge of the electronegativity of the carbonate group enhances the problem of making valid corrections to the vicinal coupling constants. In addition, since the carbonate is a bicyclic molecule, one would expect that the bond lengths and hybridizations in this molecule might deviate more than those of the diacetate from the bond lengths and hybridizations used by Karplus in his derivation.

The electronegativity of the acetate group, as noted above, is 3.72 on the scale of Dailley and Cavanaugh. The electronegativity of the carbonate group would be expected to be slightly larger than that of the acetate group, although in light of the large uncertainties involved in applying the electronegativity corrections and the inability to correct for the deviations in bond lengths and hybridizations, the electronegativity error should not be critical. Assuming a lowering of the theoretical coupling constants in the carbonate by an amount ranging from eight to 17 per cent and averaging the numbers thus found,

one obtains 7.6, 0.46, and 3.9 cps for $J_{11'}$, J_{12}, and J_{13} respectively. Substitution of these averaged corrected coupling constants into the Karplus equation yields the dihedral angles given in Table 6.

Table 6

Vicinal Coupling Constants and Dihedral Angles for the Carbonate

	J Uncorrected	J Corrected, Average	Dihedral Angle
$J_{11'}$	6.6	7.6	16°
J_{12}	0.40	0.46	108°
J_{13}	3.4	3.9	43°

With the exception of the H_1-C-C-H_1, dihedral angle, these values are unfortunately unreasonable; the H_1-C-C-H_2 and H_1-C-C-H_3 angles yield an H_2-C-H_3 bond angle of 151°, and corrections as high as 100 per cent give angles only slightly better than those given in Table 4. The H_1-C-C-H_1, dihedral angle, however, is indeed, a reasonable number. If this value is accepted as being qualitatively correct and is comapred with the H_1-C-C-$H_{1'}$ dihedral angle found for the diacetate, it is seen that the bicyclic carbonate has much more restriction on its internal freedom of motion than does the diacetate. It must be kept in mind, of course, that these dihedral angles, both for the diacetate and for the carbonate, are the time-averaged valves. The large errors involved with the caronate, however, preclude any further comparison of the conformation of

the carbonate and diacetate.

The corrections applied to the coupling constants of the carbonate are obviously too small. The dependence of the vicinal coupling constants on hybridizations and bond lengths, as well as electronegativity perturbations appear to be important in this series of compounds although the exact source (or sources) of the deviations cannot be predicted. It is interesting that J_{12} in the carbonate has decreased by approximately 39 per cent over the corresponding J_{12} in the diacetate; on the other hand, J_{13} in the carbonate has dropped by about 90 per cent over J_{13} in the diacetate (see Tables 5 and 6). The cause for the relative magnitudes of these decreases is unknown although it appears that the simple dihedral angle dependence of the vicinal coupling constants is not sufficient to explain this observation.

It is also noteworthy that there is coupling across four bonds in the carbonate whereas no such long range interaction is present in the diacetate. It may be that the carbonate is rigid enough to allow a sufficient, time-averaged, backside overlap between the C-H bonding orbitals of the protons@to the ether oxygen in the tetrahydrofuran ring to yield the interactions observed. The diacetate, on the other hand, may be too flexible to allow a large enough time-averaged backside overlap between these orbitals to yield any observable interaction (52). This explanation, it must be emphasized, is only speculation,as there is no experimental evidence either to support or to discount this rationali-

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(52) See E. O. Bishop, Ann. Rep. Progr. Chem., 58, 55 (1961); E. W. Garbish, Jr., J. Am. Chem. Soc., 86, 1710 (1964); M. J. S. Dewar and R. C. Fahey, ibid., 85, 2704 (1963).

zation. Here again, hybridizations and bond lengths may be important contributing factors, or the interactions may take place along the four single bonds.

It is disappointing that only one of the dihedral angles found for the carbonate seems reasonable, although all three of the values obtained for the diacetate appear to be qualitatively correct. An x-ray analysis of the carbonate should yield the bond lengths and bond angles of this molecule in the solid state and perhaps offer some explanation for the large deviation from the Karplus equation shown by this compound. Finally, it is noteworthy that the unusual NMR spectra of the carbonate series of compounds are consistent with the unusual reactivities characteristic of the phosphates in this carbonate series and of the ribonucleic acids themselves. Whether or not the peculiarities influencing the NMR spectra are related to those affecting the reactivities of these phosphates is debatable.

APPENDIX

MATHEMATICAL ANALYSIS OF THE NMR SPECTRA

The analyses of the NMR spectra were done by standard methods (53). The notation used here is that which is found in reference (41). This method is briefly summarized below for nuclei with a spin of 1/2.

In order to calculate the NMR spectrum of p interacting nuclei, the energy states and corresponding stationary state wave functions must be found. Each nucleus has a spin vector, $\vec{I}$, such that the spin angular momentum is given by $h\vec{I}/2\pi$ and the magnetic moment by $\gamma \frac{h}{2\pi} \vec{I}$, where h is Planck's constant and γ the gyromagnetic ratio for the given nucleus. From the general properties of quantum mechanics it follows that there is a spin quantum number, I, giving rise to $2I + 1$ possible energy states (I is 1/2 for hydrogen). In the absence of a magnetic field these $2I + 1$ states are all degenerate; the application of a magnetic field, however, destroys this degeneracy. For a nucleus of spin 1/2, I_Z, the spin quantum number for the Z component of spin angular momentum, has the value of $\pm$ 1/2. The spin function α corresponds to an I_Z of + 1/2, while the spin function β is used for an

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(53) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw Hill, Inc., New York, N. Y., (1956), Chapter 6.

I_Z of -1/2.

For an applied magnetic field in the negative Z direction and p interacting nuclei, the complete Hamiltonian, is given by equations (12-14).

$$\mathcal{H} = \mathcal{H}^{(0)} + \mathcal{H}^{(1)} \qquad \text{(Eq. 12)}$$

$$\mathcal{H}^{(0)} = \frac{1}{2\pi} \sum \gamma_i H_i I_{z(i)} \qquad \text{(Eq. 13)}$$

$$\mathcal{H}^{(1)} = \sum_{i<j} J_{ij} \vec{I}_{(i)} \cdot \vec{I}_{(j)} \qquad \text{(Eq. 14)}$$

Hi is the magnetic field at nucleus i, and Jij is the coupling constant, in cycles per second, between nuclei i and j. The other terms have their above indicated significance. The magnetic field at nucleus i, Hi, is given by equation (15).

$$Hi = Ho(1 - \sigma_i) \qquad \text{(Eq. 15)}$$

Ho is the applied field, and σ_i is the screening constant for nucleus i.

For p interacting nuclei, the 2^p orthogonal basic product functions (Eq. 16) are used to generate the stationary state wave functions (Eq. 17).

$$\psi_m = \alpha(1)\beta(2)\alpha(3)\cdots\beta \qquad \text{(Eq. 16)}$$

$$\phi_q = \sum a_{qm} \psi_m \,, \quad q = 1, 2, \cdots 2^p \qquad \text{(Eq. 17)}$$

A variation calculation (54) performed on the linear combinations of basic product functions yields the secular equation (18).

$$\left| \mathcal{H}_{mn} - E_q \delta_{mn} \right| = 0 \qquad \text{(Eq. 18)}$$

where $\delta = 0$, if $m \neq n$, $\delta = 1$ if $m = n$, $\mathcal{H}_{mn}$ are the matrix elements, and E_q are the energy states for the system. If the basic product functions are classified as to their total value of spin in the Z direction, F_Z, (Eq. 19), it can be shown that all matrix elements of the form $\mathcal{H}_{mn} = \langle \psi_m | \mathcal{H} | \psi_n \rangle$ are equal to zero when $F_Z(m) \neq F_Z(n)$ and $\mathcal{H} = \mathcal{H}^{(0)} + \mathcal{H}^{(1)}$.

$$F_Z = \sum_i I_Z(i) \qquad \text{(Eq. 19)}$$

Thus, the secular equation can be factored into $\underline{p} + 1$ separate equations of smaller degree corresponding to all possible values of F_Z. The diagonal matrix elements, $\mathcal{H}_{mn}$, of each of the $\underline{p} + 1$ equations are given by equations (20) and (21).

$$\langle \psi_m | \mathcal{H}^{(0)} | \psi_m \rangle = \frac{1}{2\pi} \sum_i \gamma_i H_i I_Z(i) \qquad \text{(Eq. 20)}$$

where $I_Z(i)$ is replaced by $\pm$ 1/2, corresponding to the correct spin function, α or β.

$$\langle \psi_m | \mathcal{H}^{(1)} | \psi_m \rangle = \frac{1}{4} \sum_{i<j} J_{ij} T_{ij} \qquad \text{(Eq. 21)}$$

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(54) C. A. Coulson, "Valence," Clarendon Press, Oxford, (1952) pages 54-67, Chapter III.

where Tij=1 if spin i equals spin j in ψ_m and = -1 if spin i is unequal to spin j in ψ_m. The off-diagonal elements are given by equations (22) and (23).

$$\langle \psi_m | \mathcal{H}^{(0)} | \psi_n \rangle = 0 \qquad \text{(Eq. 22)}$$

$$\langle \psi_m | \mathcal{H}^{(1)} | \psi_n \rangle = \tfrac{1}{2} U J_{ij} \qquad \text{(Eq. 23)}$$

U has the value of unity if ψ_m differs from ψ_n by the interchange of exactly two spins, i and j; otherwise U is zero.

With the matrix elements evaluated and the secular equation solved to give the eigenvalues, Eq, the corresponding stationary state wave functions are found as linear combinations of the basic product functions (Eqs. 16, 17). The coefficients, a_{qm}, are determined on the basis that the stationary state wave functions are normalized and that equation (24), a direct result of the variation calculation, be satisfied.

$$\sum_n \mathcal{H}_{mn} a_{qn} = E_q a_{qm} \qquad \text{(Eq. 24)}$$

Only those transitions between states which differ in their value of F_Z by ± 1 (i.e. $\Delta F_Z = \pm 1$) are allowed. The intensity of each transition is given by equation (25).

$$\text{Intensity} \propto \left(\frac{h}{2\pi}\right)^2 \left| \langle \psi_m | \sum_i \gamma_i I_x(i) | \psi_n \rangle \right|^2 \qquad \text{(Eq. 25)}$$

where ψ_m and ψ_n are the eigenfunctions for the two states of the

given transition, and Ix(i) is the component of spin angular momentum along the x-axis.

When given chemical shifts and coupling constants, the computer performs this calculation and prints out the calculated spectrum. The program, which is shown below, can calculate the spectrum of seven or less interacting nuclei of spin 1/2. This program was written especially for the Burrough's B-5000 computer.

```
                    BEGIN                                                    0000
      ALPHA A1,A2,A3,A4,A5                                          ;        0000
                                                                    START OF SEGMENT ********** 0002
    REAL F,P,Q,R,S,T,V,Z,VA,VB,VC,VG,VH,VI                          ;        0000
    INTEGER G,H,I,J,K,L,M,N,GA,GB,MM,NN                             ;        0000
    ARRAY SPIN[0:7,0:7],AA,AB[0:35,0:35],A[0:630],AE[0:35]          ;        0000
    INTEGER ARRAY MA,MB,D[0:40]                                     ;        0008
    LABEL L1,LB                                                     ;        0011
    FILE IN R1117(2,10 )                                            ;        0011
    FILE OUT W1117 1(1,15)                                          ;        0016
FORMAT FM1(",",X20,"CALCULATED PROTON MAGNETIC RESONANCE ",                  0021
                                                                    START OF SEGMENT ********** 0003
          "SPECTRUM",X53,",") ,                                              0021
      FM2(X30,5A6/X29,I2," PROTONS"//X25,"PROTON",X18,                       0021
          "CHEMICAL SHIFT" ) ,                                               0021
      FM3(X26,I2,X20,F11.2) ,                                                0021
      FM4(/X25,"PROTONS",X12,"SPIN-SPIN COUPLING CONSTANT") ,                0021
      FM5(X24,2I3,X20,F9.2) ,                                                0021
      FM6(/",",X27,"SPECTRUM",F8.1," TO",F8.1,X30,",",/X28,                  0021
          "POSITION",X12,"INTENSITY") ,                                      0021
      FM7(28(120A1 /) // 28(120A1 /) ) ,                                     0021
      FM8(I2,F8.6,3F10.2,X4,5A6 ),                                           0021
      FM9(8F10.2)                                                ;           0021
    D[1] ← 1                                                     ;           0021
                                                                    0003 IS 0136 LONG, NEXT SEG 0032
    FOR I ← 1 STEP 1 UNTIL 38 DO  D[I+1] ← 2 × D[I]              ;           0022
L1: READ(R1117,FM8,NN,E,VA,VB,VC,A1,A2,A3,A4,A5 )                ;           0025
    WRITE(W1117[D8L1 ,FM1 )                                      ;           0049
    WRITE(W1117[D8L1,FM2,A1,A2,A3,A4,A5,NN )                     ;           0053
    READ(R1117,FM9,FOR I←1 STEP 1 UNTIL NN DO                                0069
                FOR J←I STEP 1 UNTIL NN DO  SPIN[I,J] )          ;           0075
    WRITE(W1117[D8L1],FM3, FOR I ← 1 STEP 1 WHILE I ≤ NN  DO                 0085
```

```
                                    [I,SPIN[I,I] ]    )                    ;                    0094
      WRITE(W1117[OBL],F#4 )                                               ;                    0101
      WRITE(W1117[OBL],F#5, FOR I ← 1 STEP 1 WHILE I < NN  DO                                   0104
                            FOR J ← I+1 STEP 1 WHILE J ≤ NN  DO                                 0113
                                  [I,J,SPIN[I,J] ] )                       ;                    0118
      P ← 0                                                                ;                    0127
      FOR I ← 1 STEP 1 WHILE I < NN  DO                                                         0128
      FOR J ← I+1 STEP 1 WHILE J ≤ NN  DO                                                       0132
      BEGIN SPIN[J,I] ← Q ← 0.25 × SPIN[I,J]                               ;                    0137
            SPIN[I,J] ← Q ← Q                                              ;                    0140
            P ← P + Q                                 END                  ;                    0143
      GR ← 1                                                               ;                    0145
      BB[11 ← 0                                                            ;                    0147
      M4 ← 1                                                               ;                    0149
BEGIN ARRAY X[0:239]                                                       ;                    0149
                                                                                 START OF SEGMENT ********** 0004
      LABEL L2,L3,L4,L5,L6,L7                                              ;                    0002
      K ← 239                                                              ;                    0002
      FOR I ← 0 STEP 1 UNTIL K  DO X[I] ← 0                                ;                    0002
      VR ← 0.254 × VB                                                      ;                    0004
      VI ← ENTIER( 5 × VC / VB ) + 1                                       ;                    0008
      VC ← -2 / VC + 2                                                     ;                    0012
      VG ← VA - VI × VR                                                    ;                    0014
      VH ← VA + VB ×( 239 + VI )                                           ;                    0015
L2:                                                                                             0018
      G ← 0                                                                ;                    0018
      FOR I ← NN-MM+1 STEP 1 UNTIL NN DO  G ← G + D[I]                     ;                    0019
      GA ← 1                                                               ;                    0024
      BA[11 ← G                                                            ;                    0028
      IF MM=NN THEN GO TO L5                                               ;                    0029
L3:   I ← J ← NN                                                           ;                    0030
      H ← 0                                                                ;                    0032
```

```
L4: G ← G - D[I]                                                    ;   0033
    I ← I - 1                                                       ;   0034
    IF G ≥ D[I] THEN                                                    0035
    BEGIN H ← H + D[J]                                              ;   0037
          J ← J - 1                                                 ;   0038
          GO TO L4                                  END             ;   0040
    GA ← GA + 1                                                     ;   0041
    BA[GA] ← G ← G + H + D[I]                                       ;   0042
    IF H > 0 THEN  GO TO L3                                         ;   0044
    IF I > MM THEN GO TO L4                                         ;   0046
L5: FOR J ← 1 STEP 1 UNTIL GA  DO                                       0047
    BEGIN H ← K ← N ← 0                                             ;   0050
          G ← BB[J]                                                 ;   0050
          FOR I ← NN STEP -1 WHILE I > 0  DO                            0052
          BEGIN L ← D[I]                                            ;   0057
                IF G ≥ L THEN                                           0057
                BEGIN G ← G - L J H ← H + L END          ELSE           0058
                BEGIN M ← G + H + L                                 ;   0061
                      FOR K ← K + 1 WHILE BA[K] ≠ M DO              ;   0063
                      N ← N + D[K]                       END END    ;   0067
          BB[J] ← N                                      END        ;   0069
    FOR I ← 1 STEP 1 UNTIL GA  DO                                       0071
    BEGIN R ← 0                                                     ;   0075
          H ← BA[I]                                                 ;   0075
          FOR J ← NN STEP -1 WHILE J > 0  DO                            0076
          IF H ≥ D[J]  THEN                                             0081
          BEGIN H ← H - D[J]                                        ;   0082
                R ← R + SPIN[J,J]                          END      ;   0083
          A[I] ← R                                         END      ;   0086
    FOR I ← 1 STEP 1 UNTIL GA  DO                                       0088
    BEGIN R ← 0                                                     ;   0091
    H ← BA[I]                                                       ;   0091
```

```
    FOR J ← NN STEP -1 WHILE J > 0  DO                                    0092
    BEGIN L ← 1                                                           ;  0097
          IF H ≥ D[J] THEN BEGIN H ← H - D[J] ; L ← -L  END               ;  0097
          G ← H                                                           ;  0101
          FOR K ← J -1 STEP -1 WHILE K > 0  DO                               0101
          BEGIN M ← L                                                     ;  0107
                IF G > D[K] THEN BEGIN G←G-D[K]; M ← -M END               ;  0107
                IF M > 0 THEN R ← R + SPIN[J,K]                              0112
                ELSE          R ← R - SPIN[J,K]       END END             ;  0114
          A[I] ← A[I] + R                               END               ;  0118
    G ← GA                                                                ;  0121
    FOR I ← 1 STEP 1 WHILE I < GA  DO                                        0123
    FOR J ← I + 1 STEP 1 WHILE J ≤ GA DO                                     0126
    BEGIN G ← G + 1                                                       ;  0133
          H ← REAL(NOT(BOOLEAN(BA[I])EQV BOOLEAN(BA[J])) ) )              ;  0133
          FOR K ← NN STEP -1 WHILE H < D[K]  DO                           ;  0136
          H ← H - D[K]                                                    ;  0141
          FOR L ← K-1 STEP -1 WHILE H < D[L]  DO                          ;  0142
          IF H = D[L] THEN A[G] ← SPIN[L,K]                               ;  0148
          ELSE A[G] ← 0                                 END               ;  0151
    FOR I ← 1 STEP 1 UNTIL GA  DO                                            0154
    BEGIN AA[I,I] ← 1.0                                                   ;  0156
          FOR J ← I + 1 STEP 1 WHILE J ≤ GA  DO AA[I,J]←AA[J,I]←0         ;  0157
          FOR J ← I + 1 STEP 1 WHILE J ≤ GA  DO                              0165
          AA[I,J] ← AA[J,I] ← 0                         END               ;  0172
L51 L ← I ← 1                                                             ;  0177
    M ← J ← 2                                                             ;  0180
    R ← Q ← 0                                                             ;  0181
    K ← GA + 1                                                            ;  0182
    FOR H ← K STEP 1 WHILE J ≤ GA  DO                                        0184
    BEGIN R ← ABS(A[H])                                                   ;  0189
          IF R>Q THEN BEGIN Q←R; L←I; M←J; K←H          END               ;  0189
```

```
      IF J≥GA THEN I ← J ← I + 1                          ;   0194
      J ← J +1                                 END        ;   0196
IF Q < E THEN GO TO L7                                    ;   0199
Q ← A[K]                                                  ;   0200
R ← 0,5 × ( A[L] - A[M] )                                 ;   0201
IF R < 0 THEN BEGIN R ← -R ; Q ← -Q                 END   ;   0203
S ← SQRT( Q×Q + R×R )                                     ;   0207
T ← SQRT( 0,5×(1,0 + R/S) )                               ;   0209
S ← Q/(S×(T+T))                                           ;   0212
FOR I ← 1 STEP 1 WHILE I ≤ GA  DO                               0214
BEGIN Q ← AA[I,L]                                         ;   0219
      R ← AA[I,M]                                         ;   0220
      AA[I,L] ← T×Q + S×R                                 ;   0222
      AA[I,M] ← T×R - S×Q                         END     ;   0225
H ← GA - 1                                                ;   0229
I ← H + L                                                 ;   0233
J ← H + M                                                 ;   0234
FOR H ← H - 1 WHILE H>=2  DO                                    0235
BEGIN IF I ≠ K AND J ≠ K  THEN                                  0240
      BEGIN Q ← A[I]                                      ;   0242
            R ← A[J]                                      ;   0243
            A[I] ← T×Q + S×R                              ;   0244
            A[J] ← T×R - S×Q                      END     ;   0246
      IF J < K THEN I ← I + H ELSE I ← I + 1              ;   0250
      IF I ≤ K THEN J ← J + H ELSE J ← J + 1       END    ;   0253
Q ← A[L]                                                  ;   0258
R ← A[M]                                                  ;   0259
Z ← A[K]                                                  ;   0260
V ← T × S                                                 ;   0261
S ← S × S                                                 ;   0262
T ← T × T                                                 ;   0263
A[K] ← Z × (T-S) + V × (R-Q)                              ;   0265
```

```
    V ← Z × ( V + V )                                                    ;    0268
    A[L] ← T × Q + S × R + V                                             ;    0272
    A[M] ← T × R + S × Q - V                                             ;    0273
    GO TO L6                                                             ;    0277
L7: IF MM = 1 THEN BEGIN AE[1] ← P ;  AB[1,1] ← 1      END               ;    0278
    FOR G ← 1 STEP 1 UNTIL GB  DO                                             0283
    FOR H ← 1 STEP 1 UNTIL GA  DO                                             0285
    BEGIN R ← A[H] - AE[G]                                               ;    0286
    IF VG < R AND R ≤ VH  THEN                                                0286
    BEGIN                                                                     0289
    Q ← 0                                                                ;    0290
    FOR I ← 1 STEP 1 UNTIL GB  DO                                             0290
    BEGIN                                                                     0292
    K ← BB[I]                                                            ;    0292
    FOR J ← GA STEP -1 WHILE J > 0  DO                                        0292
    BEGIN L ← D[J]                                                       ;    0297
          IF K ≥ L  THEN                                                      0297
          BEGIN K ← K - L                                                ;    0299
                Q ← Q + AB[I,G] × AA[J,H]          END END END           ;    0299
    M ← ENTIER((R-VA)/VB)                                                ;    0305
    K ← M - VI                                                           ;    0310
    IF K < 0 THEN K ← 0                                                  ;    0311
    L ← M + VI                                                           ;    0313
    IF L > 239 THEN L ← 239                                              ;    0314
    Q ← Q + 2                                                            ;    0316
    S ← VA + K × VB                                                      ;    0317
    FOR I ← K STEP 1 WHILE I ≤ L DO                                           0319
    BEGIN X[I] ← X[I] + Q × EXP( VC × (R-S) ↑ 2 )                        ;    0323
          S ← S + VB                          END  END  END              ;    0328
    FOR I ← 1 STEP 1 UNTIL GA DO                                              0335
    BEGIN BB[I] ← BA[I]                                                  ;    0337
    FOR J ← 1 STEP 1 UNTIL GA  DO  AB[I,J] ← AA[I,J]                     ;    0337
```

```
      AE[I] ← AF[I]                                    END        ;                    0342
   MM ← MM + 1                                                   ;                    0346
   GG ← GA                                                       ;                    0349
   IF MM ≤ NN THEN GO TO L2                                      ;                    0350
   WRITE(#1117[PAGE])                                            ;                    0351
   Q ← R ← 0                                                     ;                    0355
   FOR I ← 0 STEP 1 UNTIL 239 DO                                                      0356
   BEGIN R ← X[I]                                                ;                    0358
      IF R > Q THEN Q ← R                                 END    ;                    0359
   R ← 29.5 / Q                                                  ;                    0363
   FOR I ← 0 STEP 1 UNTIL 239 DO X[I] ← R × X[I]                 ;                    0364
   WRITE(#1117,F47,FOR I ← 28 STEP -1 UNTIL 1 DO FOR J ← 120 STEP                     0371
                 1 UNTIL 239 DO IF X[J] > I THEN "*" ELSE " ",                        0377
                 FOR I ← 28 STEP -1 UNTIL 1 DO FOR J ←   0 STEP                       0386
                 1 UNTIL 119 DO IF X[J] > I THEN "*" ELSE " " ))                      0388
                                                       END    ;                    0400
   WRITE(#1117[PAGE]     )                                       ;                    0400
                                                                   0004 IS 0404 LONG, NEXT SEG 0002
   GO TO L1                                                      ;                    0153
L99                                                              ;                    0154
                                    END                          .                    0155
                                                                   0002 IS 0158 LONG, NEXT SEG 0001

EXP IS SEGMENT NUMBER 0005,PRT ADDRESS IS 0114
SQRT IS SEGMENT NUMBER 0006,PRT ADDRESS IS 0113
OUTPUT(W) IS SEGMENT NUMBER 0007,PRT ADDRESS IS 0104
OUTPUT(C) IS SEGMENT NUMBER 0008,PRT ADDRESS IS 0103
INPUT(W) IS SEGMENT NUMBER 0009,PRT ADDRESS IS 0102
INPUT(C) IS SEGMENT NUMBER 0010,PRT ADDRESS IS 0077
FILE CNTRL(W) IS SEGMENT NUMBER 0011,PRT ADDRESS IS 0016
FILE CNTRL(C) IS SEGMENT NUMBER 0012,PRT ADDRESS IS 0015
READ/WRITE IS SEGMENT NUMBER 0013,PRT ADDRESS IS 0014

NUMBER OF ERRORS DETECTED = 000,  COMPILATION TIME = 0025 SECONDS.
```